CALIBER – A phase II randomised feasibility study of **C**hemoresection and surgic**A**l management in **L**ow r**I**sk non muscle invasive **B**ladder canc**ER**

PROTOCOL

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Chief Investigator:	Mr Hugh Mostafid
Sponsor:	The Institute of Cancer Research
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The CALIBER trial has been approved
by the National Institute for Health Research
The CALIBER trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio

ICR The Institute of Cancer Research

NHS National Institute for Health Research

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

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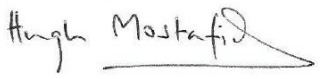
The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and Principal Investigators from a subset of participating sites. A copy of the current membership of the TMG can be obtained from the CALIBER Trial Manager at ICR-CTSU.

Protocol Authorised by:

Name & Role	Signature	Date
Mr Hugh Mostafid (Chief Investigator)		20/06/2017

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

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

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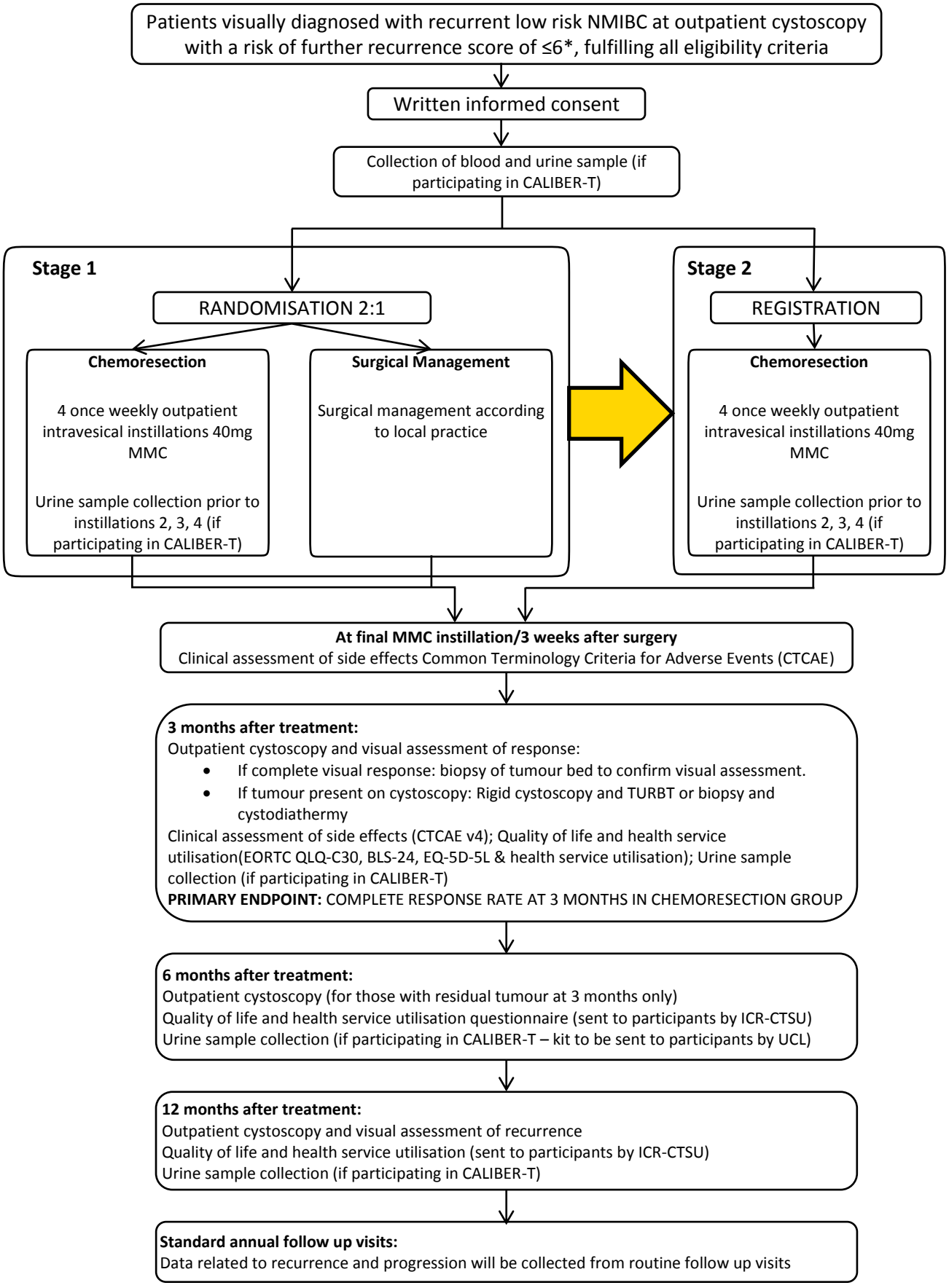
CALIBER TRIAL SUMMARY

PROTOCOL TITLE	A phase II randomised feasibility study of chemoresection and surgical management in low risk non muscle invasive bladder cancer.
TARGET DISEASE	Low risk non muscle invasive bladder cancer.
STUDY OBJECTIVES	Primary objective: To demonstrate that chemoresection has sufficient activity against NMIBC to warrant further investigation of its role as a potential alternative to surgical intervention for low risk NMIBC recurrence. Secondary objectives: To collect further information to support development of a subsequent phase III study, including: • Providing evidence of feasibility of recruitment • Providing data regarding acceptability and feasibility of chemoresection treatment delivery by assessment of treatment compliance • Providing an indication of sample size which would be required for a phase III study by assessing time to recurrence in patients disease free at 3 months • Collecting prospective data on surgical management currently in use at trial sites • Estimating trans-urethral resection or biopsy rates in both treatment groups • Estimating progression-free survival • Assessing side effects of both treatments using clinician reported toxicity scales • Assessing side effects and impact of both treatments on patient reported quality of life (QL) • Collecting prospective data on length of stay in hospital due to surgical treatment • Providing an indication of health service utilisation as a result of both treatments
STUDY DESIGN	Randomised multicentre two stage phase II feasibility study. In stage 1 patients are randomised (2:1) to chemoresection or surgery. In stage 2 all patients receive chemoresection
TRIAL POPULATION	Patients with recurrent low risk (Ta G1 or Ta G2 (Ta low grade)) NMIBC who have a risk of further recurrence score of ≤6.
RECRUITMENT TARGET	Stage 1: 51 chemoresection participants; 26 surgery participants; Stage 2: 9 chemoresection participants. Total: 89 participants (including a 5% inflation for drop out in chemoresection group)
TREATMENT REGIMEN	Chemoresection group: 4 once weekly instillations of 40mg MMC as outpatients. Surgical management group: Standard surgical management in use at treating hospital for treatment of recurrence.

PRIMARY ENDPOINT	In the chemoresection group: Complete response to chemoresection 3 months post-treatment.
SECONDARY ENDPOINTS	In the chemoresection group: • Treatment compliance In both groups: • Time to recurrence in patients disease free at 3 months • Transurethral resection and biopsy rates • Progression-free survival • Toxicity • Quality of life • Health service utilisation
FEASIBILITY ENDPOINT	Feasibility of patient recruitment
FOLLOW UP	For both groups: Adverse event assessment 3 weeks from start of treatment (at last MMC instillation for chemoresection group); cystoscopy at 3 months then annually. For patients with residual tumour at 3 month cystoscopy - rigid cystoscopy and TURBT or biopsy and cystodiathermy of tumour as appropriate with further check cystoscopy 3 months later.
TRANSLATIONAL SAMPLE COLLECTION	CALIBER participants will be asked to consent to provide the following samples: • Blood sample • Urine samples at baseline, during chemoresection (if applicable), 3 months, 6 months, 12 months and recurrence (if applicable) • Routinely obtained diagnostic formalin fixed paraffin embedded (FFPE) tumour tissue from histologically confirmed diagnosis. FFPE tissue from first recurrence following randomisation will also be collected (if applicable)

TRIAL SCHEMA



* See A3 CALIBER RISK CALCULATION TABLE (adapted from EAU Guidelines[12])

1. INTRODUCTION

1.1. Background

Bladder cancer is the seventh most common cancer in the UK, with 10,324 people diagnosed in 2010[1]. Bladder cancer can be divided into two groups, non-muscle invasive bladder cancer (NMIBC), where the cancer is confined to the lining of the bladder and muscle invasive bladder cancer, where the cancer has spread deeper to involve the muscle wall of the bladder and beyond. The latter is a life threatening condition for which radical treatment is required.

Patients with NMIBC are categorised as low, intermediate and high risk depending on risk factors for subsequent progression to invasive disease[2]. Approximately 49% of all patients with bladder cancer have low risk NMIBC[3], representing about 5,000 new patients per year in the UK. Although at very low risk of progression to MIBC (0.8-6% at 5 years[2]), relatively high local recurrence rates of 46-62% at 5 years, with half of these occurring in the first year of follow-up, mean that the discomfort and inconvenience of treating NMIBC recurrence is the main issue for patients rather than the risk of progression or death from bladder cancer.

Schedules to monitor for recurrent low risk NMIBC developed by the European Association of Urology (EAU) recommend that 3 months after surgical treatment patients should have an outpatient cystoscopy to visually assess for recurrent disease[2]. Correlation between visual assessment by cystoscopy and histological findings is high, with cystoscopy correctly predicting the tumour stage and grade of 93% of low risk NMIBC[4]. If no recurrent disease is detected, outpatient cystoscopies are conducted 9 months later and annually for 5 years[2]. If recurrence is found it is not possible to remove it at outpatient cystoscopy and the patient is readmitted for surgical management of the recurrence under general or spinal anaesthetic, 2-4 weeks after visual diagnosis.

It has been found that failure rates for surgical management vary between surgeons. A combined analysis of seven European Organisation for Research and Treatment of Cancer (EORTC) studies reported visible tumour at three months in 26.6% of patients after resection of multiple tumours[5] (a similar group to the low risk patients included in CALIBER).

In considering research opportunities in low risk NMIBC, a patient survey was developed by the CALIBER Chief Investigator to identify the most bothersome aspects of the condition. 100 patients with low risk NMIBC participated. 87% of participants stated they were reassured by regular outpatient surveillance for recurrence by cystoscopy, however 66% disliked inpatient surgical management of recurrence under general anaesthetic and would prefer a non-surgical outpatient option.

Whilst distinct treatment strategies have evolved over the last decade for intermediate and high risk groups[2], management of recurrent low risk NMIBC is less well defined. Current standard of care for recurrent low risk NMIBC should be surgical intervention[6,7], however a survey conducted of centres interested in participating in CALIBER revealed that no clear surgical management strategy exists for the low risk group. Some centres resect recurrences whilst others cauterise them, with surgery mainly carried out under general anaesthetic. It therefore seems timely, given the prioritisation of the topic by patients and the variety in practice between centres, to focus research efforts on defining the standard of care and reducing the burden of treatment in low risk NMIBC.

1.2. Chemoresection in the treatment of NMIBC

Treatment with 6 sessions of chemotherapy instilled into the bladder is recommended after surgery for patients with NMIBC at intermediate risk of recurrence or progression[2]. Several small studies have shown promising results with chemotherapy alone (chemoresection) but the optimal schedule and the effectiveness of chemoresection in completely clearing all cancer present (complete response (CR)) is unclear for low risk NMIBC[8]. Two reviews of chemoresection included over 1,200 patients in all three NMIBC risk groups and described a number of different chemotherapy agents given in 4-8 instillations. On average, CR was 50%, with the therapeutic effect sustained for at least 2 years[8,9]. Patients with

intermediate risk NMIBC showed a CR of 67% in response to one agent[8]. These data indicate that chemoresection alone may be a viable treatment for those with low risk NMIBC.

1.3. Known risks and benefits of mitomycin C (MMC)

Side effects of intravesical MMC chemotherapy are well characterised as this treatment has been in use for NMIBC for around 25 years. Because the drug remains in the bladder with little getting into the bloodstream, the main side effects are bladder irritation and pain and frequency of urination. These side effects tend to resolve within 24-48 hours of treatment. About 1 in 10 people also develop a short term rash on their hands and feet and around 1 in 100 will develop a urine infection which can be treated with antibiotics.

The benefit of MMC is that it is a treatment that can be delivered on an outpatient basis and may remove the need for surgical intervention.

1.4. Known risks and benefits of surgical intervention

Surgical removal/ablation of a tumour has risks associated both with the operation on the bladder, and with the delivery of general anaesthetic. Immediate common side effects of the operation include discomfort passing urine once the catheter is removed or developing a urine infection. Around 1 in 100 patients experience significant blood loss in the urine which necessitates a blood transfusion, or bladder perforation which requires catheter drainage. In rare instances open surgery is required in order to repair a bladder perforation. A small amount of blood can continue to be visible in the urine for up to 2 weeks after treatment of the tumour, and patients are advised to avoid any heavy lifting, sports, sexual activity or driving a car during this time.

Surgical intervention is the standard of care within this patient population.

1.5. Study rationale

Patients diagnosed with low risk NMIBC are at risk of frequent low grade recurrence, which usually necessitates surgical intervention under general anaesthetic. CALIBER is a multicentre study which aims to establish the short term efficacy of chemoresection in the treatment of NMIBC. Should the levels of complete response following chemoresection meet predefined criteria, a larger phase III trial would be developed to assess longer term disease related endpoints, with the aim of standardising management of recurrent low risk NMIBC and potentially removing the need for over a thousand patients each year to undergo surgery.

2. TRIAL OBJECTIVES

2.1. Primary objective

To demonstrate that chemoresection has sufficient activity against NMIBC to warrant further investigation of its role as a potential alternative to surgical intervention for low risk NMIBC recurrence.

2.2. Secondary objectives

To collect further information to support development of a subsequent phase III study, including:

- Providing evidence of feasibility of recruitment
- Providing data regarding acceptability and feasibility of chemoresection treatment delivery by assessment of treatment compliance
- Providing an indication of sample size which would be required for a phase III study by assessing time to recurrence in patients disease free at 3 months
- Collecting prospective data on surgical management currently in use at trial sites
- Estimating subsequent transurethral resection and biopsy rates in both treatment groups

- Estimating progression-free survival
- Assessing side effects of both treatments using clinician reported toxicity scales
- Assessing side effects and impact of both treatments on patient reported quality of life (see Appendix A1)
- Collecting prospective data on length of stay in hospital and number of days of work missed due to treatment
- Providing an indication of health service utilisation as a result of both treatments

3. TRIAL DESIGN

CALIBER is a two stage phase II, multicentre, randomised controlled trial (RCT). A control group has been included to provide prospective data about surgical management and outcomes and assess feasibility of recruitment to a randomised study.

Stage 1: 80 patients will be recruited with treatment allocated 2:1 by randomisation between chemoresection (n=54 (including 5% non-evaluable rate)) and surgical management (control; n=26).

Stage 2: If the stop/go activity criteria at the end of stage 1 indicate that recruitment should continue, 9 additional participants will be recruited, all of whom will receive chemoresection.

Patients assigned to the chemoresection group will receive 4 once weekly intravesical instillations of 40mg MMC as outpatients.

Patients assigned to the surgical management group will receive the standard surgical management in use at their hospital for treatment of recurrence which may include a single post-operative instillation of 40mg MMC within 24 hours.

All participants will be followed up at 3 weeks from treatment (i.e. from final MMC instillation for chemoresection group) and each will receive a cystoscopy three months from the end of treatment to assess response, in accordance with EAU guidelines. Subsequent cystoscopic follow up will take place 12 months after treatment if recurrence-free at 3 months and then annually.

4. STUDY ENDPOINTS

4.1. Primary endpoint

Complete response to chemoresection 3 months post-treatment.

4.2. Secondary endpoints

In the chemoresection group:

- Treatment compliance

In both groups:

- Time to recurrence in patients disease free at 3 months
- Transurethral resection and biopsy rates
- Progression-free survival
- Toxicity
- Quality of life
- Health service utilisation

4.3. Feasibility endpoints

Feasibility of patient recruitment

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of participants

The aim is to recruit 89 participants; with 63 patients in the chemoresection group (stage 1 plus stage 2) and 26 patients in the surgical management (control) group (stage 1 only).

5.2. Source of participants

Participants will be recruited from approximately 25 participating sites in the UK. Potential participants will be identified by their clinical care teams following a visual diagnosis of recurrent low risk NMIBC at outpatient cystoscopy under local anaesthetic, prior to subsequent admission for surgical management. Discussion at multidisciplinary team (MDT) meetings, will aid identification of potential participants. Patients for whom CALIBER is a suitable option will be approached and will be given time to consider participation.

5.3. Inclusion criteria

1. Written informed consent
2. NMIBC recurrence following original diagnosis of low risk NMIBC (defined as Ta G1 or Ta G2 (Ta low grade) with a risk of recurrence score of ≤6 using EORTC risk tables (see Appendix A3 - CALIBER RISK CALCULATION TABLE)).
3. Histologically confirmed TCC at original diagnosis
4. Aged 16 or over
5. Satisfactory haematology values haemoglobin > 100 g/L and serum creatinine < 1.5xULN
6. Negative pregnancy test for women of child-bearing potential

5.4. Exclusion criteria

1. Any history of: grade 3/high grade or ≥T1 transitional cell carcinoma, concomitant carcinoma in situ, more than 7 tumours at one diagnosis or more than 1 recurrence per year since initial diagnosis or in the past five years, whichever is shorter (see Appendix A3 - CALIBER RISK CALCULATION TABLE)
2. Any history of histologically confirmed non-TCC bladder cancer
3. Trial entry recurrence identified within 11.5 months of the date of the original diagnosis
4. Any prior treatment of the trial entry recurrence (including biopsy)
5. Previous MMC chemotherapy other than a single instillation at diagnostic surgery
6. Known allergy to MMC
7. Carcinoma involving the prostatic urethra or upper urinary tract (participants should have had imaging of the upper urinary tract within 2 years prior to randomisation)
8. Known or suspected reduced bladder capacity (<100ml)
9. Significant bleeding disorder
10. Female patients who are breast-feeding or are of childbearing potential and unwilling or unable to use adequate non-hormonal contraception. Male patients should also use contraception if sexually active.
11. Active or intractable urinary tract infection
12. Urethral stricture or anything impeding the insertion of a catheter
13. Large narrow neck diverticula
14. Significant urinary incontinence
15. Any other conditions that in the Principal Investigator's opinion would contraindicate protocol treatment
16. Unable or unwilling to comply with study procedures or follow up schedule

5.5. Life style guidelines

Female participants must be surgically sterile or be post-menopausal, or must agree to use effective contraception during the period of therapy and for 30 days after the last dose of study treatment.

Male participants must be surgically sterile or must agree to use effective contraception during the period of therapy and for 30 days after the last dose of study treatment.

Effective contraception is defined as double barrier contraception (e.g. condom plus spermicide in combination with a diaphragm, cervical cap or intrauterine device).

6. SCREENING

6.1. Screening log

During stage 1, all participating sites will be required to keep a log of all participants with visually diagnosed recurrent low risk NMIBC who are potentially eligible for this study. The information collected on the log will include:

- Date of initial diagnosis
- Date patient identified with recurrence
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Trial ID (if applicable)

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

Sites are not required to complete screening logs during stage 2 of the trial.

6.2. Procedure for obtaining informed consent

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

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

Patients who consent to CALIBER will be asked to consent to participate in the CALIBER quality of life and health service utilisation study and CALIBER-T (for further details see Appendices 1 & 2). Patients should be made aware that participation in the sub-studies is entirely voluntary. Refusal to participate will not preclude participation in the main clinical trial and will not impact the medical care received.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

6.3. Participation in other clinical trials

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

CALIBER patients will not be permitted to participate in any other trials of investigational medicinal products whilst they are being treated within CALIBER and until the 3 month post treatment cystoscopy has been performed.

Participation in other clinical trials will be considered on a case by case basis by the Trial Management Group.

7. TRIAL ENTRY

Stage 1:

Patients in stage 1 must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should be randomised by telephoning ICR-CTSU on:

020 8643 7150

09.00-17.00 (UK time) Monday to Friday

Randomisation should take place within 30 days prior to the planned start date of treatment. An eligibility and randomisation checklist must be completed prior to registration.

The following information will be required at randomisation:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for trial and for any sub-studies;
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number

The caller will be given the patient's unique randomisation number (Trial ID) and treatment allocation (see section 9).

ICR-CTSU will send confirmation to the data management contact and pharmacist (if allocated chemoresection) at the recruiting site to confirm a patient's entry into the trial.

Stage 2:

Participants in stage 2 must be registered centrally with the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should be registered by telephoning ICR-CTSU on:

020 8643 7150

09.00-17.00 (UK time) Monday to Friday

Registration should take place within 30 days prior to the planned start date of treatment. An eligibility and registration checklist must be completed prior to registration.

The following information will be required at registration:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for trial participation and for any sub-studies
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number

The caller will be given the patient's unique registration number (Trial ID).

All registered CALIBER participants will receive chemoresection (see section 9).

ICR-CTSU will send confirmation to the data management contact and pharmacist at the recruiting site to confirm a patient's entry into the trial.

8. TRIAL ASSESSMENTS

8.1. Pre-randomisation assessments

The following assessments should be conducted within 30 days prior to randomisation for all patients:

- Physical examination
- Haematology & biochemistry
- Pregnancy test for females of childbearing potential
- Quality of life (EORTC QLQ-C30, BLS24, EQ-5D-5L)

In addition, participants should have received an upper urinary tract imaging within the previous two years.

8.2. Pre-treatment assessments

The following assessments should be conducted within 60 days before treatment start for all patients:

- Physical examination
- Haematology & biochemistry
- Symptom assessment (CTCAE V4 [10])
- Pregnancy test for females of childbearing potential

If participating in CALIBER-T:

- EDTA blood sample
- Provision of urine sample home collection kit

Study treatment (MMC) should be discontinued in women found to be pregnant (see Section 8.6).

8.3. Chemoresection instillation

The following assessment should be conducted prior to each MMC instillation for chemoresection patients:

- Pregnancy test for females of childbearing potential

Study treatment (MMC) should be discontinued in women found to be pregnant (see Section 8.7).
If participating in CALIBER-T:

- Provision of urine sample home collection kit prior to instillations 2, 3 and 4.

8.4. End of treatment assessments

The following information relates to end of treatment assessments applicable to patients recruited in stage 1 of the trial:

Adverse events (CTCAE V4, and Clavien Dindo[11] grade (for surgical group only, see Appendix A4 - CLAVIEN-DINDO GRADING SYSTEM FOR THE CLASSIFICATION OF SURGICAL COMPLICATIONS)) should be assessed for each participant 3 weeks post-surgery (for those in the surgical group) or at the time of the final MMC instillation (for participants in the chemoresection group).

The following information relates to end of treatment assessments applicable to patients recruited in stage 2 of the trial:

Adverse events (CTCAE V4) should be assessed for each participant at the time of the final MMC instillation.

8.5. Post-treatment follow-up - from end of MMC course or post-surgery

8.5.1. 3 months post treatment

- Flexible cystoscopy and visual assessment of response (see Appendix A5- Response criteria).
- Biopsy of tumour bed to confirm visual assessment of complete response
- Quality of life and health service utilisation questionnaire (EORTC QLQ-C30, BLS24, EQ-5D-5L, health service utilisation)
- Adverse event assessment (CTCAE v.4)

If participating in CALIBER-T:

- Provision of urine sample home collection kit

If residual/recurrent tumour found at cystoscopy:

- Rigid cystoscopy and TURBT or biopsy and cystodiathermy of tumour as appropriate. Tumour sample should be obtained for histological analysis.

8.5.2. 6 months post treatment

- Outpatient cystoscopy (for patients with residual tumour at 3 months only)
- Quality of life and health service utilisation questionnaire (EORTC QLQ-C30, BLS24, EQ-5D-5L, health service utilisation) (administered by ICR-CTSU)

If participating in CALIBER-T:

- Urine sample home collection kit will be sent to patient's home by University College London

8.5.3. 12 months post treatment

- Outpatient cystoscopy
- Quality of life and health service utilisation questionnaire (EORTC QLQ-C30, BLS24, EQ-5D-5L, health service utilisation) (administered by ICR-CTSU)

If participating in CALIBER-T:

- Provision of urine sample home collection kit

8.5.4. Annually thereafter

Participants should be followed up annually according to EAU guidelines[12].

8.6. Procedure at disease progression/recurrence

Participants should be treated according to local clinical judgement at disease progression/recurrence. Subsequent data relating to disease recurrence or progression will be collected from the patient's standard annual surveillance visits.

8.7. Discontinuation from treatment or follow-up

Participants may discontinue trial treatment at any time at their own request, or treatment may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation will include:

- Disease progression
- Unacceptable toxicity

- Pregnancy

Participants who discontinue treatment should continue to be followed up. If a patient withdraws consent for further follow-up it should be clarified whether they no longer wish to attend trial specific follow up visits or wish to stop contributing further data to the study. A trial deviation form should be completed for any patient who withdraws consent for information to be sent to the ICR-CTSU or for attending trial follow up visits. In the very rare event that a patient requests that their data is removed from the study entirely, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing.

8.8. Schedule of assessments

Visit/Assessment	Pre-randomisation (within 30 days of randomisation)	Pre-treatment (within 60 days before treatment)	At each chemoresection instillation	3 weeks post surgery/at final MMC instillation	3 months after completion of treatment	6 months after completion of treatment	12 months after completion of treatment	Annually thereafter	Disease progression /recurrence
Physical examination	X	X						According to EAU guidelines	Treatment according to local clinical practice
Haematology and biochemistry	X	X							
Pregnancy test for women of childbearing potential	X	X[1]	X						
Upper urinary tract imaging (if not conducted within the previous two years)	X								
Symptom/adverse event assessment (CTCAE V4 and Clavien Dindo[2])		X		X	X				
Outpatient flexible cystoscopy with biopsy of tumour bed					X[3]				
Rigid cystoscopy and TURBT or biopsy and cystodiathermy if residual tumour at 3 month assessment					X				
Outpatient flexible cystoscopy						X[4]	X		
Quality of Life (QL) questionnaire (EORTC QLQ C30, BLS24, EQ-5D-5L & Health service utilisation)	X				X	X[5]	X[5]		
Provide home urine collection kit[6]		X	X		X	X[7]	X		
EDTA blood sample [6]		X							

Footnotes

1. If randomised to the chemoresection group
2. Surgical management group at 3 weeks post-surgery only (stage 1 only)
3. If complete visual response at 3 months
4. For patients with residual tumour at 3 months only
5. To be administered by ICR-CTSU
6. For patients who have consented to CALIBER-T only
7. To be supplied directly to participant by UCL

9. TRIAL TREATMENT

Mitomycin C (MMC) is the investigational medicinal product within CALIBER.

9.1. Surgical management

The following information relates to the surgical intervention, randomisation to which will close following completion of stage 1:

Patients assigned to the surgical management group will receive the standard surgical management in use at their hospital for treatment of recurrence. This can include trans-urethral resection of bladder tumour (TURBT) or biopsy and cauterisation (diathermy) of the tumour under general or spinal anaesthetic or laser ablation of the tumour under local anaesthetic. Patients will need to be admitted to hospital for the operation which will take 20-40 minutes. A catheter may be left in situ in order to drain and flush the bladder post-operatively. In accordance with EAU guideline recommendations, patients may receive a single instillation of 40mg intravesical MMC post-operatively. Patients may require an overnight stay and will be able to go home once the catheter has been removed and they are able to urinate successfully.

9.2. Chemoresection

Patients assigned to the chemoresection group will receive 4 once weekly intravesical instillations of 40mg MMC as outpatients.

9.2.1. Dose and schedule

Four once weekly intravesical instillations of 40mg MMC, delivered via catheter under local anaesthetic. Dose modifications are not permitted.

Instillations may be optimised by asking the patient to restrict their fluid intake for up to 6 hours before the instillation and ensuring that the bladder has been completely emptied via the catheter prior to instillation. There should not be a gap of more than 14 days between instillations. This treatment can be delivered by an appropriately trained nurse specialist.

9.2.2. Duration of MMC treatment

For patients undergoing chemoresection, outpatient visits to clinic will be required over 4 weeks. Once the MMC has been instilled into the bladder and the catheter has been removed, patients will be able to leave hospital (according to local practice). The MMC needs to be held in the bladder for one hour after instillation, after which patients can urinate. Patients should be informed of appropriate safety and hygiene precautions when urinating at home following treatment.

9.2.3. Discontinuation

The instillations should be discontinued following any serious adverse event which requires a change of treatment, or any incidence of a suspected allergic reaction to MMC - particularly the development of a skin rash on the palms of the hand and soles of the feet. Any treatment delays and discontinuation are at the discretion of the investigator.

9.2.4. Subsequent therapy

All patients will undergo a flexible cystoscopy at 3 months following completion of treatment. Patients with complete visual response should have biopsy of the tumour site to confirm response by histology. Patients with suspected or obvious residual tumour should undergo rigid cystoscopy and TURBT or biopsy and cystodiathermy of tumour as appropriate.

9.3. Supportive care

Supportive care should be given in accordance with local clinical practice. It is suggested that patients experiencing an allergic reaction to MMC can be offered oral antihistamines. Irritative bladder symptoms can be managed by anticholinergic therapy. Patients with proven urinary tract infection should be treated with the appropriate antibiotics. All supportive care must be recorded in the patient's notes, as well as the appropriate pages of the CRF.

9.4. Concomitant therapy

All medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the study drugs may be given at the discretion of the investigator. All concomitant medications must be recorded in the patient's notes, as well as the appropriate pages of the CRF.

9.5. Drug supplies, labelling and pharmacy responsibilities

MMC should be prescribed by the investigator and prepared and dispensed from hospital pharmacy from hospital stock, in accordance with local guidelines for the safe handling of cytotoxics, for the duration of the trial. MMC stock should be obtained from usual drug suppliers in accordance with local practice.

In addition to the local pharmacy label, the dispensed drug should be labelled in accordance with the MHRA approved CALIBER label. Drug formulation, storage, accountability and destruction should be in accordance with local policy. MMC should be stored at room temperature, in a safe and secure place. ICR-CTSU should be provided with confirmation of the local pharmacy's clinical trial drug handling and destruction procedures. Further information regarding MMC can be found in the Summary of Product Characteristics (SmPC).

10. PHARMACOVIGILANCE

10.1. Definitions

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient or clinical trial subject administered a study treatment; the event does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after the commencement of study treatment and within 30 days of the last administration and:

1. results in death,
2. is life-threatening
3. requires hospitalisation or prolongation of existing inpatients´ hospitalisation
4. results in persistent or significant disability or incapacity
5. is a congenital anomaly or birth defect

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

Progression of the indicated disease and death due to progression of the indicated disease are not considered SAEs.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

Serious Adverse Reaction (SAR)
A serious adverse reaction is an SAE that is suspected as having a causal relationship to the study treatment as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Definitions of causality

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

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A serious adverse reaction to the investigational medicinal product, the nature or severity of which is not consistent with the safety information provided in the applicable Summary of Product Characteristics (SmPC) and is assessed as unexpected by the Chief Investigator.

Related Unexpected Serious Adverse Event
An adverse event occurring in the surgical group that meets the definition of serious and is assessed by the CI or nominative representative as:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence

10.2. Reporting Adverse Events to ICR-CTSU

Any symptom that occurs after commencement of study treatment and within 30 days of the last administration of study treatment, which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant CRF and forwarded to ICR-CTSU.

The severity of AEs should be graded according to CTCAE criteria. For each symptom, the highest grade observed since the last visit should be reported.

Whenever one or more symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

10.3. Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs from the commencement of study treatment and up to 30 days following the last administration of study treatment must be reported.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated clinical representative) becoming aware of the event, by completing the CALIBER SAE form and sending to:

The ICR-CTSU safety desk

Fax no: 0208 722 4368

Email: SAE-icr@icr.ac.uk

For the attention of the CALIBER Trial team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available.

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

10.3.1. Reporting of Serious Adverse Events to ICR-CTSU

The following information relates to the surgical intervention, randomisation to which will close following completion of stage 1:

The following adverse events related to surgery are considered expected if grade ≤4 and do not require reporting on an SAE form. Instead the event should be recorded using the appropriate CRF:

- Bladder discomfort or pain
- Urinary frequency
- Haematuria
- Urinary retention requiring catheterisation
- Infection of bladder requiring antibiotics
- Delayed bleeding requiring removal of clots or further surgery
- Damage to drainage tubes from kidney (ureters) requiring additional therapy
- Injury to urethra causing delayed scar formation
- Perforation of the bladder requiring a temporary urinary catheter or open surgical repair

If any of the above events are grade 5 they should be reported on an SAE form within 24 hours of the investigator becoming aware of the event.

10.4. Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all reported SAEs for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality).

SAEs assessed as having a causal relationship to study treatment and as being unexpected will undergo expedited reporting to the relevant authorities by ICR-CTSU (see Figure 1 for SAE reporting).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

10.5. Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA and the main REC within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA and the main REC within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA and the main REC as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting sites will be informed of any SUSARs occurring within the trial at regular intervals.

10.5.1. Expedited Reporting of Related Unexpected SAEs

If an SAE is identified as being related to surgery and unexpected by the Chief Investigator it will be reported by ICR-CTSU to the main REC, the Sponsor and all other interested parties within 15 days of being notified of the event.

The Principal Investigators at all actively recruiting sites will be informed of any related unexpected SAEs occurring within the trial at appropriate intervals.

10.6. Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator becomes aware of the outcome.

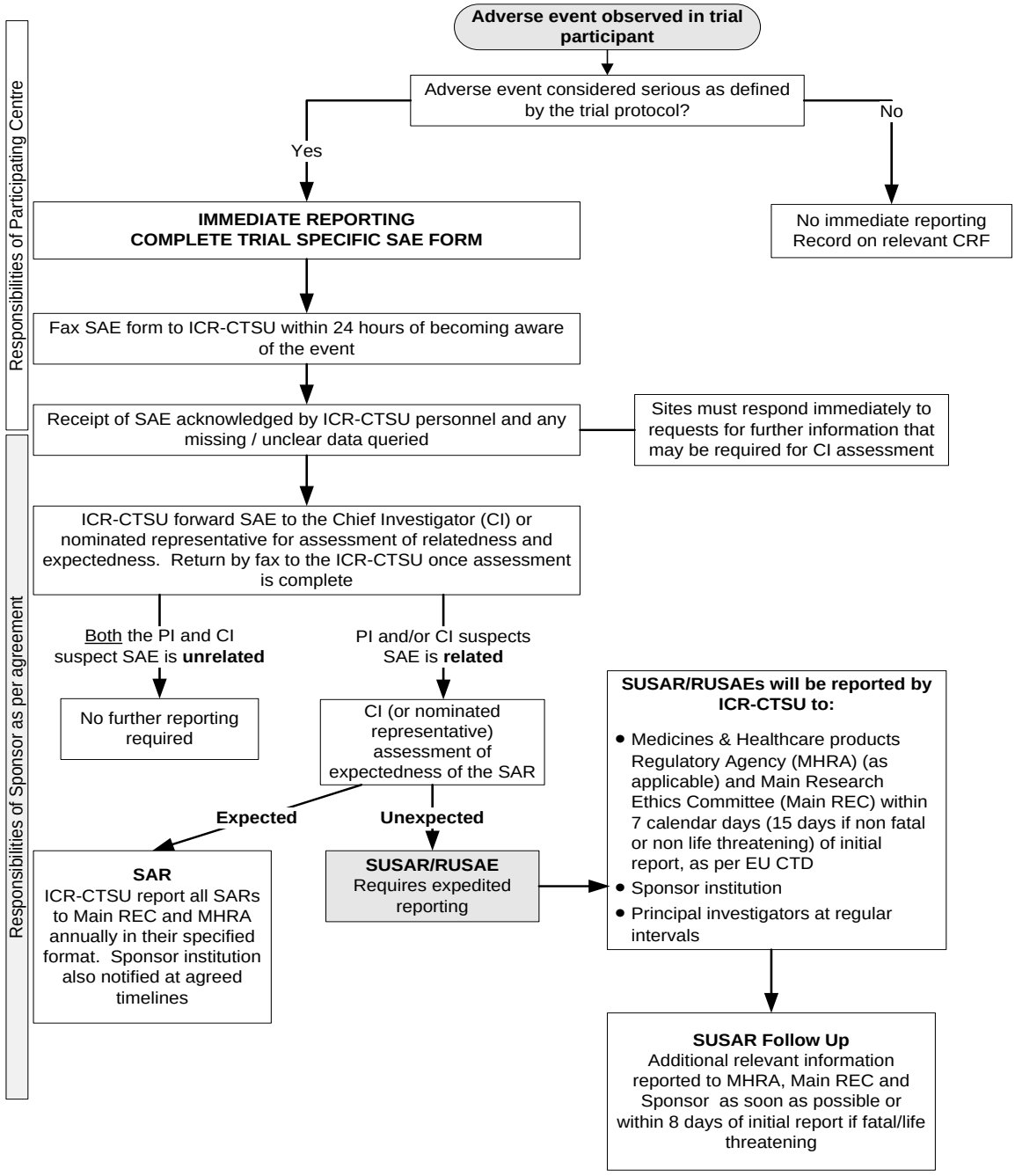
10.7. Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and the main REC by ICR-CTSU.

10.8. Reporting pregnancies

If any trial patient or a trial participants' partner becomes pregnant while receiving study treatment or up to 30 days after treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discontinue from trial treatment immediately. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

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



NB. All SAEs should continue to be followed up as specified above

11. STATISTICAL CONSIDERATIONS

11.1. Statistical Design and Sample Size Justification

CALIBER was designed as a multi-centre, randomised controlled, phase II trial. Allowing for a 5% non-compliance rate and inclusion of a control group, it aimed to randomise 174 patients to the trial using an experimental:control ratio of 2:1.

The sample size for CALIBER was initially determined based on the assessment of the primary endpoint in the chemoresection group using a Simon's 2 stage phase II design. A control group has been included to provide prospective data about surgical management and outcomes and assess feasibility of recruitment to a randomised study. The trial is designed to assess complete response (CR) in the chemoresection group and is not adequately powered to conclude non-inferiority of time to recurrence in the chemoresection group. Randomisation has therefore been weighted 2:1 to the chemoresection group to maximise information in the experimental group whilst providing contemporaneously collected information in an unbiased control group to enable informal comparisons that will support development of a phase III trial.

Following consultation with patient representatives, CALIBER has been designed to exclude a CR rate of less than 45%. This is on the basis that if the CR rate is less than 45%, chemoresection would not be an attractive alternative to surgical management as it would delay rather than prevent surgical intervention in the majority of patients and hence would be unlikely to reduce the burden of treatment of recurrence. If the CR rate is >60% then the strategy of chemoresection would warrant further investigation. Using a Simon's 2 stage phase II optimal design (to allow early stopping for futility) with α=0.05, 90% power, p0=0.45, p1=0.60 the required sample size is 51 chemoresection patients in the first stage. If fewer than 26 CRs are seen in chemoresection patients in the first stage, then recruitment would cease (there having been no previous break in recruitment, to allow determination of CR in stage 1 patients, on completion of accrual to stage 1). At the end of the second stage, if at least 58/110 chemoresection patients have a CR then it would be concluded that chemoresection demonstrated adequate activity to warrant further investigation. Inflating to account for 5% noncompliance, and to include a control group, this gives a total target recruitment of 174 patients, 116 in the chemoresection group (54 in stage 1; 62 in stage 2) and 58 in the surgical management group (27 in stage 1; 32 in stage 2).

11.1.1. Modification to stage two of the trial design

Due to slower than anticipated accrual and with approval of the independent Trial Steering Committee (TSC) the 2 stage trial design has been adapted. This adaption has been made without knowledge of the CR rate in stage 1 i.e. prior to the decision to stop/go at the completion of stage 1. Based on good acceptance rates amongst eligible patients (approximately 56% as at February 2017 as reported on screening logs) the TSC recommended that the control group could be dropped for stage 2 – the feasibility of randomisation being proven during stage 1. To address recruitment timelines, the TSC advised that the overall power and significance levels could be relaxed, whilst maintaining the original stage 1 decision rule, to achieve a reduced overall total sample size.

Following completion of recruitment to stage 1 (51 evaluable chemoresection patients) and in the absence of any safety concerns raised by the Independent Data Monitoring Committee, recruitment to stage 2 will commence with all patients receiving chemoresection. With 51 chemoresection patients recruited in stage 1 and an additional 9 chemoresection patients recruited in stage 2, the adapted 2-stage Simon design retains p0=0.45 and p1=0.60 and the threshold for activity at stage 1 (stop/go criteria) of at least 26 responders in 51 chemoresection patients and provides 85% power and 10% one-sided significance. If at the end of stage 2, at least 31/60 chemoresection patients have a CR then it would be concluded that chemoresection demonstrated adequate activity to warrant further investigation.

Therefore, nine additional chemoresection patients will be required in stage 2 (giving a total of 60 chemoresection patients) with an overall target sample size of 89 patients, including the control group patients at stage 1 (26 patients) and allowing a 5% drop out (unevaluable) rate in the chemoresection group.

11.2. Treatment allocation

In stage 1, Participants will be randomised between chemoresection and surgical management on a 2:1 basis.

Treatment allocation is by minimisation with a random element; balancing factors will be listed in the statistical analysis plan.

In stage 2, all participants will receive chemoresection.

11.3. Endpoint definitions

11.3.1. Primary endpoint

Complete response to chemoresection 3 months post treatment in the chemoresection group is defined as an absence of any tumour following chemoresection. Response will be assessed visually at check cystoscopy by patients' urologists and a biopsy of the tumour bed will take place to confirm visual assessment of complete response.

11.3.2. Secondary endpoints

In the chemoresection group:

- Treatment compliance. Patients who receive 4 MMC instillations with no more than 14 days between each instillation will be described as fully compliant.

In both groups:

- Time to recurrence in patients disease free at 3 months, defined as time from randomisation to time of first local or distant recurrence.
- Recurrence free interval, defined as time from end of treatment to first relapse, in patients confirmed recurrence free at 3 months.
- Subsequent TURBT /biopsy rate.
- Progression free survival, defined as time from randomisation to the first of muscle invasive bladder recurrence, recurrence in the pelvic nodes, distant metastatic recurrence or death from any cause.
- Toxicity (NCI CTCAE V4) with a particular focus on bladder spasm, haematuria, urinary frequency, urinary retention, urinary tract pain. Clavien Dindo grade collected (in surgical group).
- Quality of life as measured by EORTC QLQ-C30 and BLS24 questionnaires. Domains of interest include global health / QL, functioning domains, urinary symptom scales and items relating to side effects associated with MMC and surgical management
- Health service utilisation as measured by the HSU questionnaire.

11.3.3. Feasibility endpoint

Feasibility of patient recruitment

Recruitment milestones have been set as follows (based on at least 25 centres being open by the end of month 18):

- 15 participants by the end of month 6,
- 42 by the end of month 12
- 91 by the end of month 18.

11.4. Statistical analysis plan

Feasibility of recruitment will be assessed against recruitment milestones using descriptive methods and will be monitored by the Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC) throughout the duration of the trial.

Complete response (CR) is defined as an absence of any tumour following chemoresection and will be assessed visually at check cystoscopy by patients' urologists with histological confirmation by biopsy. Patients with visual disease, or positive histology where visually clear will not be considered as responding. Concordance between visual and histological response will be examined; the aim being to confirm that visual responders are true histological responders. CR and transurethral resection and biopsy rates in the chemoresection group will be calculated together with 95% CI using exact methods. Because the primary endpoint is non-comparative, it is planned to include all patients commencing chemoresection in the primary calculation of response to chemoresection. If it is the case that patients in the surgical group require further surgical intervention following the 3 month check cystoscopy, the rate of re-resection will be calculated in this group (with the corresponding 95% CI) to allow informal comparisons to be made of the rate of surgical intervention post initial treatment between the two groups.

Compliance with treatment will be summarised by the number of instillations received in the chemoresection group and by the number of patients switching between treatment groups. Acute and late toxicity will be summarised by the proportions experiencing grade ≥3 side effects with comparisons made using chi-squared based tests or Fisher's exact test if expected cell frequencies are less than 5. In addition, methods for ordinal data will be used. Standard algorithms will be used to derive scores from and handle missing data in QL questionnaires. Treatment groups will be compared at individual timepoints and analyses to account for the longitudinal nature of the data (generalised estimating equations) may be used. A health service utilisation analysis will be undertaken from the resource usage perspective of the UK NHS. Health outcomes will be assessed in terms of quality adjusted life-years (QALYs). A within-trial analysis will use trial data to report QALYs and other endpoints.

Time to event endpoints will be analysed by the logrank test and summarised by a HR with 95% CI. The principal timepoint of interest is 1 year; estimates of event rates will be calculated using the Kaplan-Meier method with the HR from Cox model to estimate the CI for the difference. The Cox proportional hazard model will be used to adjust for stratification factors. Methods to account for non-proportionality will be used if appropriate.

Sensitivity analyses of the primary endpoint including patients who receive all 4 MMC instillations ("full treatment compliance"), all patients allocated chemoresection (irrespective of whether it was received) and patients otherwise non-evaluable will also be performed. Further details of analysis methods and analysis populations will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

11.5. Interim Analyses and Stopping Rules

The trial has a 2-stage modified optimal design. If 25 or fewer responses are seen in the first 51 evaluable chemoresection patients the trial would be stopped for futility. An Independent Data Monitoring Committee will review emerging safety and efficacy data at the end of the first stage and at least annually and will advise on evaluability. Unless data collected as the trial is on-going suggest it would be unsafe, it is proposed that recruitment continues whilst the analysis of the first stage is conducted. Due to the well-defined safety profile of MMC, as discussed above, severe toxicity is not anticipated and thus no a priori early stopping rule for toxicity has been defined. Any decisions to halt the trial due to emerging safety data would be taken by the Independent Data Monitoring Committee.

12. TRIAL MANAGEMENT

12.1. Trial management group (TMG)

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

12.2. Trial steering committee (TSC)

A Trial Steering Committee (TSC) will be set up and will include an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. The TSC will meet annually. The TSC will provide expert independent oversight of the trial on behalf of the funder. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

12.3. Independent data monitoring committee (IDMC)

An IDMC will be instigated to monitor the progress of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

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

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

13. RESEARCH GOVERNANCE

13.1. Sponsor responsibilities

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

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

14. TRIAL ADMINISTRATION & LOGISTICS

14.1. Site activation

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

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and, if applicable, a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate. ICR-CTSU will provide the final confirmation that recruitment can commence at a site

14.2. Data acquisition

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

14.3. Central data monitoring

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

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

14.4. On-site monitoring

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

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

14.5. Completion of the Study and Definition of Study End Date

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

14.6. Archiving

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

15. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

15.1. Trial approvals

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

The trial has received ethical approval from a research ethics committee (REC) for multi-centre trials, regulatory approval from the MHRA and global R&D approval via the NIHR Coordinated System for gaining NHS Permission. Before entering patients, the Principal Investigator at each site is responsible for obtaining confirmation of local approval to conduct the trial.

15.2. Trial conduct

This trial will be conducted in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, the Research Governance Framework for Health and Social Care and the principles of GCP.

15.3. Informed consent

Patients should be asked to sign the current main REC approved CALIBER consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current main REC approved CALIBER patient information sheets (PIS) should be provided to patients in addition to any standard patient information sheets that are provided by the site and used in routine practice.

15.4. Patient confidentiality

Patients will be asked to consent to their full name being collected at randomisation in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples.

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

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

15.5. Data protection act (DPA)

ICR-CTSU will comply with all applicable data protection laws.

15.6. Liability

ICR has in force a non-fault compensation insurance for any potential injury caused in connection with participation in this clinical trial. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to ICR's insurers, via the ICR Purchasing office.

16. FINANCIAL MATTERS

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

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

17. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating

clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

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

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

18. ASSOCIATED STUDIES

18.1. Quality of life & health service utilisation study

Quality of Life (QL) will be a secondary endpoint in the main trial and will be analysed as described in the statistical analysis plan.

Further details are provided in Appendix A1 - QUALITY OF LIFE & HEALTH SERVICE UTILISATION STUDY.

18.2. CALIBER translational studies (CALIBER-T)

Patients will be asked to donate urine samples which will be used to investigate potential diagnostic biomarkers. Urine samples are provided using home collection kits and shipped to the receiving lab using pre-paid packaging.

Patients will also be asked to donate a blood sample to provide germline DNA to allow comparison with their tumour sample. This blood sample can be taken at any time point from patients who consent to provide this sample after joining CALIBER. Blood collection tubes are provided and shipped to the receiving lab using pre-paid packaging.

Consent will also be sought for access to routinely collected diagnostic paraffin blocks from original diagnosis and subsequent recurrences.

For further details of CALIBER-T, see Appendix A2 - TRANSLATIONAL SUBSTUDY (CALIBER-T)

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A1. QUALITY OF LIFE & HEALTH SERVICE UTILISATION STUDY

A1.1 Background

The primary outcome of CALIBER is complete response to chemoresection 3 months post treatment in the chemoresection group. Quality of life (QL) is being assessed as a secondary endpoint.

A1.2 Hypothesis

It is hypothesised that participants receiving chemoresection will experience fewer side effects and this will result in higher global quality of life score than that of those participants receiving surgical intervention. It is also hypothesised that patients receiving chemoresection will have higher scores on the functional scales and report fewer grade 3 or 4 urinary symptoms than patients undergoing surgical management.

A1.3 Quality of life and health service utilisation measures

Quality of life will be assessed using the EORTC Quality of Life Questionnaire (QLQ-C30) version 3 [13], BLS24[14] and EQ-5D-5L[15].

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

BLS24 is an EORTC QLQ module designed for patients with NMIBC tumours and includes scales assessing urinary symptoms and sexual function as well as bowel symptoms. It addresses problems specific to intravesical therapy and continuous cystoscopic follow up. This instrument has been used in a number of clinical trials and has undergone scale validity analysis.

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

Health service utilisation (HSU) will be recorded by patient recall questionnaire covering visits to : hospital, GP/Nurse, A&E/Casualty and telephone consultations to health care professionals. Any private medical care received would be self-reported and collected together with the approximate cost to the patient.

A1.4 Study design

Patients are eligible for the QL & HSU assessment in this study if they fulfil the eligibility criteria and complete the baseline questionnaire before randomisation. Participants will be informed in the patient information sheet (PIS) that they will receive questionnaires regularly while involved in this trial. QL & HSU are secondary endpoints, evaluated in a longitudinal design in all patients entered in this study.

A1.5 Timing of data collection

Patients will be asked to complete questionnaires within 14 days prior to randomisation. Patients will be asked to fill out the questionnaires as completely and accurately as possible. The average time to complete the entire questionnaire is 10-15 minutes. Baseline and 3 month booklets will be administered by the centre and two further booklets will be sent to patients' homes by the ICR-CTSU at 6 and 12 months. This will total four questionnaires per participant. The target timeframe for

completion of follow up questionnaires will be +/- two weeks of the scheduled follow-up assessment.

A1.6 Compliance

Missing data may hamper assessment of QL in clinical trials. This may be because questionnaires are not administered or returned at the appropriate time (unit non-response), or because patients may miss questions within the questionnaires (item non-response). Item non-response occurs less than 2% [16] on average with the QLQ-C30 instrument and should not be a problem. Unit non-response 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 QL assessment. At 6 months from randomisation the follow up assessments will be co-ordinated by the ICR-CTSU who will send postal questionnaires to the patient. One reminder will be made with a second questionnaire (including a stamped addressed envelope). During the study, compliance with completing questionnaires – unit and item non-response, will be monitored.

A1.7 Statistical considerations

The primary endpoint for assessing QL is the global health/quality of life subscale. According to the EORTC reference manual [16], for this subscale a difference of 8 points is considered clinically relevant & standard deviation for genitourinary cancers is 22.2 points.

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

Analyses of HSU data will be largely descriptive; data returns will be summarised and estimates of health service costs will be calculated using national tariffs. Services used will be summarised by treatment group and, where appropriate, average cost to the NHS and cost to the patients will be compared between the two groups. If data are complete enough, cost-effectiveness may be considered in terms of quality adjusted life years.

A2. TRANSLATIONAL SUBSTUDY (CALIBER-T)

A2.1 Introduction

CALIBER participants will be asked to provide prospective consent for access to routinely collected tumour and bladder tissue in formalin fixed paraffin blocks. Participants will also be asked to donate one blood sample and sequential urine samples at those centres participating in CALIBER-T.

Samples will be used to identify and investigate potential diagnostic, predictive and prognostic biomarkers and the pathogenesis of non-muscle invasive bladder cancer as part of separately funded translational research.

Participation in CALIBER-T is optional and patients will be asked to provide written informed consent at the time of trial entry. Participants who do not consent to CALIBER-T will still be able to join the CALIBER trial.

A2.2 CALIBER-T urine collection

Patients at centres participating in CALIBER-T will be asked to provide a pre-treatment (chemoresection/surgical management) urine sample, a sample prior to each subsequent chemoresection treatment (if applicable) and following the 3, 6 and 12 month visits. Samples should also be provided at recurrence.

Patients should be provided with a urine sample collection kit to take home, together with pre-paid packaging and instructions for postage. Sample kits will be provided by University College London upon request.

The 6 month post treatment sample kit will be posted directly to participants' home addresses by University College London.

A2.2.1. Urine sample shipping and storage

Urine samples should be shipped on the day the sample is provided using the postal kit provided by University College London. Urine samples will be stored at University College London.

Details of the urine sample collection process, including kit provision, labelling and transportation are provided in the CALIBER-T guidance notes, available on request from ICR-CTSU.

A2.3 CALIBER-T blood sample collection

Patients at centres participating in CALIBER-T will be asked to provide a single 9ml EDTA whole blood sample. If possible this sample should be collected prior to treatment at the same time as routine blood tests to minimise inconvenience to participants, however the sample can be provided at any point during trial follow up.

A2.3.1. Blood sample shipping and storage

Blood samples should be sent on the day the sample is provided using the postal kit provided by ICR-CTSU. Blood samples will be sent to and stored at the University of Leeds.

Participating centres will be provided with 9ml EDTA blood bottles, protective mailing tubes, pre-paid packaging and instructions for postage. Details of the blood sample collection process, including kit provision, labelling and transportation are provided in the CALIBER-T guidance notes, available on request from ICR-CTSU.

A2.4 CALIBER-T FFPE tissue collection

Patients at centres participating in CALIBER-T will be asked to provide prospective consent for access to routinely collected tumour and bladder tissue in formalin fixed paraffin blocks. Tissue will be collected from a histologically confirmed primary diagnosis preceding trial entry, recurrent tumour obtained as part of surgical management following trial entry (if allocated) and from the first recurrence following trial treatment (including residual tumour at 3 months which was unresponsive to MMC).

FFPE tumour tissue will be requested retrospectively and will be sent to and stored at the University of Leeds.

A2.5 Governance and data linkage

Responsibilities of the ICR, UCL and University of Leeds are defined in agreements between the parties. Samples will be stored at the receiving laboratories in accordance with their local standard operating procedures.

All samples will be pseudonymised upon receipt with a unique specimen number. Linkage to clinical data will only be possible by ICR-CTSU.

A2.6 CALIBER-T custodianship and access arrangements

As Sponsor, The Institute of Cancer Research, on behalf of the CALIBER Trial Management Group, are the custodians of the biological samples collected within CALIBER-T. Trial biospecimens will be registered on the appropriate national databases.

A3. CALIBER RISK CALCULATION TABLE (adapted from EAU Guidelines[12])

Clinical and histological details used to confirm risk of recurrence; shaded areas denote tumour features which are ineligible for inclusion in CALIBER:

Factor	Recurrence risk score
No. of tumours	
Single	0
2–7	3
≥8	6
Tumour diameter	
<3cm	0
≥3cm	3
Average annual recurrence rate¥	
Primary	0
≤1 recurrence per year	2
>1 recurrence per year	4
Category	
Ta	0
T1	1
Concomitant CIS	
No	0
Yes	1
Grade (*1973 WHO; $2004 WHO)	
G1* or low grade$	0
G2*	1
G3* or high grade$	2

Category and grade from the patient's original diagnosis and features from the current visual diagnosis of recurrence (no. of tumours, diameter and recurrence rate) should be used to calculate risk score. To be eligible for CALIBER patients must have a recurrence risk score of ≤6.

If **any** prior diagnoses exhibit known high risk features (eg>7 tumours, ≥T1, grade 3*/high grade$) the patient will not be eligible for CALIBER.

¥ Average annual recurrence rate

All prior recurrences throughout the duration of the patient's disease history, including those treated with diathermy (or similar) for which there is no histological confirmation, should be used to assess the patient's risk group.

If patients have an average annual recurrence rate of greater than 1 they are ineligible. Patients diagnosed with a recurrence within 11.5 months of their first diagnosis of bladder cancer are ineligible.

Patients with an average annual recurrence rate of 1 or less are eligible for CALIBER. Average annual recurrence rate should be calculated as follows:

$$Average\ annual\ recurrence\ rate = \frac{Total\ no.\ observed\ recurrences}{Lifetime\ of\ disease\ (months)} \times 12$$

Definitions:

Total no. observed recurrences: Total number of all observed recurrences, including the current trial entry recurrence. It does not include the first diagnosis of bladder cancer.

Lifetime of disease: Total number of months observed between the date of the original diagnosis and the date the trial entry recurrence was identified.

For the purposes of calculating average annual recurrence, if a patient's first diagnosis of bladder cancer was over five years prior to the identification of the trial entry recurrence, the lifetime of disease should be calculated for the past 60 months, including only recurrences observed during this time.

A4. CLAVIEN-DINDO GRADING SYSTEM FOR THE CLASSIFICATION OF SURGICAL COMPLICATIONS

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention.
Grade III-a:	Intervention not under general anaesthesia.
Grade III-b:	Intervention under general anaesthesia.
Grade IV:	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.
Grade IV-a:	Single organ dysfunction (including dialysis).
Grade IV-b:	Multi-organ dysfunction.
Grade V:	Death of a patient.
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

A5. RESPONSE CRITERIA

Response criteria	**Evaluation of lesions**
Complete visual response	Complete visual disappearance of all tumours
Histological/Pathological response	No evidence of malignancy in TURBT or biopsy specimen
Progressive Disease (PD)	Increase in size or number of tumours
Stable Disease (SD)	No change in tumour size or number

A6. GLOSSARY

A&E	Accident & Emergency
AE	Adverse Event
ANCOVA	Analysis of Covariance
CHI	Community Health Index
CI	Chief Investigator
CIS	Carcinoma In Situ
CR	Complete Response
CRF	Case Report Form
DCF	Data Capture Form
DPA	Data Protection Act
EAU	European Association of Urology
eCRF	Electronic Case Report Form
EDTA	Ethylene-diamine-tetra-acetic Acid
EORTC	European Organisation for Research and Treatment of Cancer
FFPE	Formalin-Fixed, Paraffin-Embedded
g/L	Gram per litre
GCP	Good Clinical Practice
Hb	Haemoglobin
HR	Hazard Ratio
HSU	Health service utilisation
ICR	The Institute Of Cancer Research
ICR-CTSU	The Institute Of Cancer Research – Clinical Trials and Statistics Unit
IDMC	Independent Data Monitoring Committee
MDT	Multi-Disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MIBC	Muscle Invasive Bladder Cancer
MMC	Mitomycin C
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCRI	National Cancer Research Institute
NHS	National Health Service
NIHR	National Institute for Health Research
NIHR CRN	National Institute for Health Research Clinical Research Network
NMIBC	Non Muscle Invasive Bladder Cancer
PD	Progressive Disease
PI	Principal Investigator
PIS	Patient Information Sheet
QALYs	Quality Adjusted Life-Years
QL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
Ta	Non-invasive papillary carcinoma
TCC	Transitional Cell Carcinoma

TMG	Trial Management Group
TSC	Trial Steering Committee
TURBT	Trans-urethral Resection of Bladder Tumour
UKCRC	UK Clinical Research Collaboration
ULN	Upper Limit of Normal
WHO	World Health Organisation