Combination chemotherapy versus Bacillus Calmette-Guérin (BCG) for high-risk non-muscle invasive bladder cancer– a phase III multi-centre randomised controlled trial

PROTOCOL

Version: 4.0

Dated: 20/01/2026

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Sponsor:	The Institute of Cancer Research
Funder:	National Institute for Health and Care Research Health Technology Assessment (NIHR-HTA)
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU)
	The Institute of Cancer Research
REC Reference Number:	25/SC/0262
IRAS Project Number:	1008661
CPMS ID:	57987
ICR-CTSU Protocol Number:	ICR-CTSU/2024/10091
Sponsor Number:	CCR6195
ISRCTN:	92816346
NIHR Reference Number:	NIHR160459

The COBRA trial has been approved by National Institute for Health Research and is part of the National Institute for Health Research Clinical Research Network Trial Portfolio.

FUNDED BY NIHR | National Institute for Health and Care Research

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This study is funded by the NIHR Health Technology Assessment programme (NIHR160459). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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This protocol describes the COBRA 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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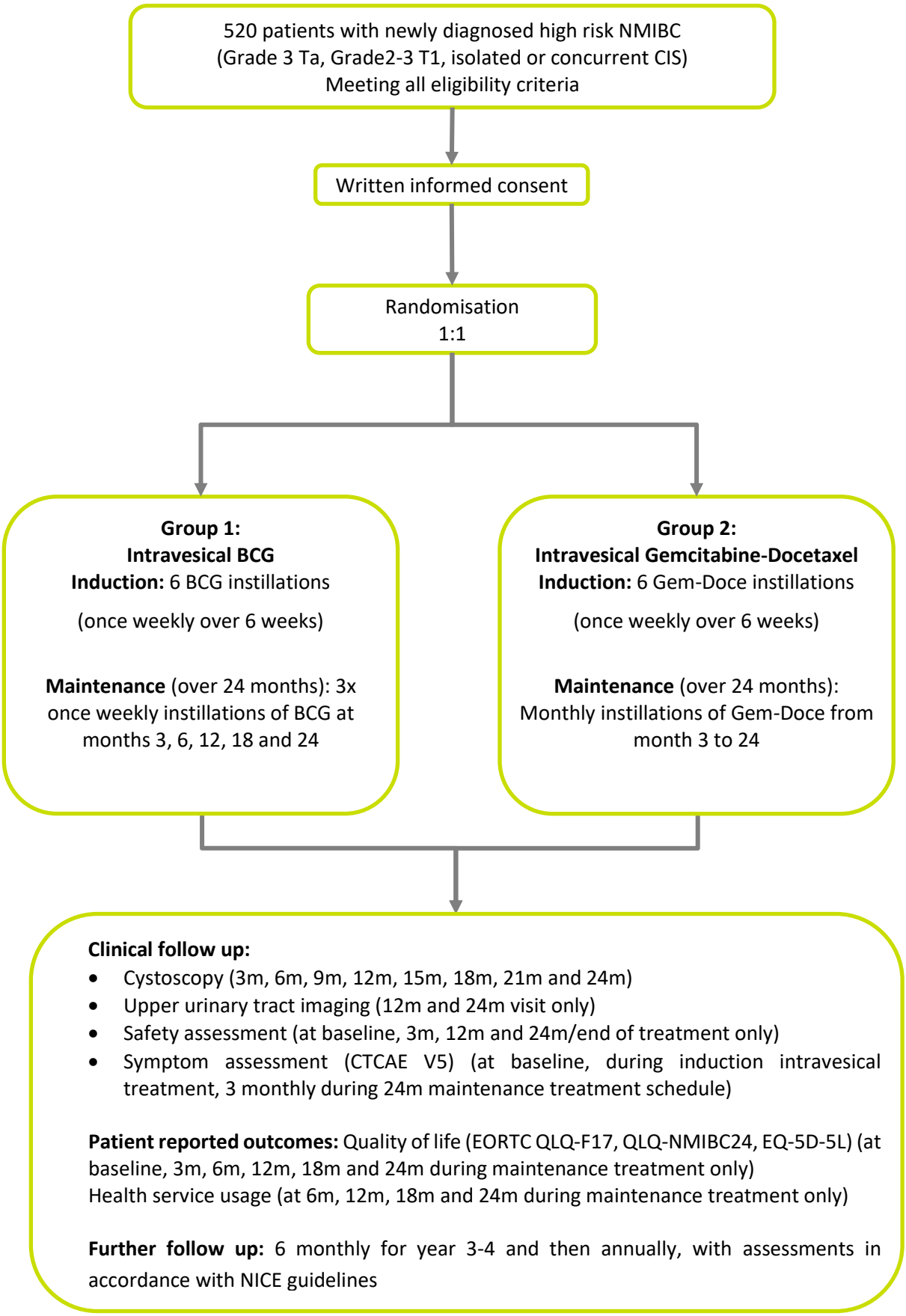
COBRA TRIAL SUMMARY

PROTOCOL TITLE	Combination chemOtherapy versus Bacillus Calmette-Guérin (BCG) for high-Risk non-muscle invasive blAdder cancer – a phase III multi-centre randomised controlled trial (COBRA).
TARGET DISEASE	Bladder cancer
TRIAL OBJECTIVES	• To determine if gemcitabine-docetaxel (Gem-Doce) is non-inferior to BCG for high-risk non-muscle invasive bladder cancer (HR-NMIBC) in terms of high grade recurrence-free survival (hgRFS). • To compare recurrence-free survival (RFS), progression-free survival, cystectomy-free survival, cancer-specific survival and overall survival of Gem-Doce and BCG. • In the subgroup of patients with primary carcinoma in situ at trial entry, to compare complete response rate at 6 months between Gem-Doce and BCG. • To compare the compliance and tolerability of both treatments. • To compare patient-reported health related quality of life during follow-up. • To estimate quality adjusted life years (QALYs) over the 24-month maintenance visit follow-up period and extrapolated over the patient lifetime. • To determine outcomes of patients developing high grade recurrence following allocated treatment who then receive the alternative, non-allocated treatment.
TRIAL DESIGN	Pragmatic phase III randomised controlled trial with internal pilot.
TRIAL POPULATION	People with a new HR-NMIBC diagnosis receiving treatment within the NHS.
RECRUITMENT TARGET	520 participants (1:1 allocation).
TREATMENT REGIMEN	Participants will be randomised in a 1:1 ratio to the following: **Control Group:** BCG bladder instillations (6 once-weekly induction instillations followed by 3 once-weekly maintenance instillations at 3, 6, 12, 18 & 24 months). **Experimental Group:** Gem-Doce bladder instillations (six once-weekly induction instillations followed by once-monthly maintenance instillations from 3 to 24 months).
PRIMARY ENDPOINT	The primary endpoint is time to earliest date of identification of high grade recurrent disease (including disease progression), metastatic disease or death from any cause.
SECONDARY ENDPOINTS	• Recurrence-free survival • Progression-free survival • Cystectomy-free survival • Cancer-specific survival / overall survival • Complete response rate at 6 months (in participants with carcinoma in situ at baseline only)

	• Number of instillations received • Clinician assessed adverse events • Patient-reported outcomes – health related quality of life • Costs to the NHS and personal social services • Cost-effectiveness
EXPLORATORY ENDPOINT	High grade recurrence following allocated treatment in participants who then receive the alternative, non-allocated treatment.
TRANSLATIONAL SAMPLE COLLECTION	Prospective consent will be requested for access to routinely collected bladder tumour tissue in formalin fixed paraffin blocks. Samples will be used in future research of non-muscle invasive bladder cancer as part of separately funded translational research.
FOLLOW UP	Clinical follow-up to 2 years post-treatment will inform the primary analysis. Thereafter, all participants will be followed-up according to NICE guidelines.

TRIAL SCHEMA



1. INTRODUCTION

1.1. Background

In the UK, approximately 4,800 people are diagnosed with high-risk non-muscle invasive bladder cancer (HR-NMIBC) annually.[1]

Bacillus Calmette-Guérin (BCG) is the only known treatment to reduce recurrence and progression of HR-NMIBC and has been in use for nearly 40 years.[2] After surgery to remove the tumour (transurethral resection of bladder tumour – TURBT), BCG is instilled into the bladder (intravesical treatment) once a week over an induction period of six weeks, followed by regular maintenance instillations given for up to three years. Due to the intensive monitoring and treatment schedules required, NMIBC is one of the most expensive cancers for the NHS to manage, with annual spending estimated to be >£210 million.[3]

1.2. Known Risks and Benefits of BCG and Gem-Doce

Identifying an alternative treatment option for HR-NMIBC is essential because of poor treatment tolerability, moderate efficacy, and periodic shortages of BCG supply. BCG causes local side effects including cystitis, increased urinary frequency, pain on urination and blood in the urine. It also causes systemic side effects including fever, malaise, flu-like symptoms and reactive arthritis. There is no test for BCG tolerability and complications can be life threatening, including sepsis and severe urinary symptoms necessitating bladder removal surgery (cystectomy). Cystectomy has a 50% complication rate, a 3% 90-day risk of death and patients have to adapt to life without a bladder afterwards, using either a stoma and bag to collect urine, or an intestinal bladder substitute.[4] Side effects of BCG accumulate over the long maintenance phase of treatment, resulting in up to 80% of patients not completing their planned schedules, compromising effectiveness.[5]

Despite BCG treatment, risk of cancer recurrence and progression to muscle invasive bladder cancer remains as high as 50% and 20% respectively at 5 years, requiring cystectomy or radiotherapy.[6] The clinical priority is to prevent high grade recurrence following BCG therapy. High grade recurrence increases likelihood of progression to muscle invasive disease which can be fatal, with a mortality rate as high as 60% at 2 years even with cystectomy.[7]

International shortages of BCG over the last decade are a concern for bladder cancer patients.[8] When BCG is unavailable, patients are either overtreated with cystectomy, or undertreated with shorter BCG courses or single agent intravesical chemotherapy, leading to worse cancer outcomes.[9]

Intravesical gemcitabine-docetaxel (Gem-Doce) was pioneered by COBRA collaborator Prof Michael O'Donnell (University of Iowa) and was developed as a rescue (salvage) treatment for high grade recurrence after BCG therapy, as an alternative to cystectomy.[10] Due to excellent tolerability and efficacy of Gem-Doce, compounded with BCG supply shortages, USA urologists have largely adopted Gem-Doce for BCG naïve patients based on retrospective data. It is now the most commonly used treatment in the USA when BCG is unavailable.[11]

While intravesical docetaxel is not used in the UK, the use of intravesical gemcitabine for bladder cancer is not new. A historic Cochrane review concluded that gemcitabine may be more active with a lower toxicity profile compared to mitomycin C, the most commonly used intravesical chemotherapy in the UK. [12]

1.3. Description of Population

Globally, bladder cancer is most common in southern (15.3 per 100,000) and western (13.0 per 100,000) Europe with men disproportionally more likely to develop bladder cancer compared to women (4:1).[13] Tobacco smoking and occupational carcinogen exposure including aromatic amines from the paint, dye, rubber, metal and petroleum industries are key risk factors for the development of bladder cancer [14]. Patients with Lynch syndrome, who have germline mutations in DNA mismatch repair genes, represent the only hereditary cancer syndrome associated with a higher bladder cancer risk. [15] Chronic inflammation attributed to recurrent urinary tract infection (UTI), chronic bladder catheterisation and schistosomiasis infection increase the risk of bladder cancer.[16] Bladder cancer incidence is associated with socio-economic disadvantage,[17] disproportionately affecting people historically underserved by research.[18] Bladder cancer

research has been consistently underfunded relative to incidence,[19] receiving only 1.1% of non-commercial funding awards globally between 2016-2020[20] despite being the 10th most common cancer worldwide.[21]

1.4. Study Rationale

There is an urgent need to identify an alternative treatment for people with HR-NMIBC that is at least as safe and effective as BCG. COBRA will assess effectiveness and cost-effectiveness of Gem-Doce for people being treated in the NHS for newly diagnosed HR-NMIBC.

Widespread dissemination of results, including amongst the patient communities who have long called for alternatives to BCG, will influence clinical practice. If non-inferiority, cost-effectiveness and fewer side effects relative to BCG are confirmed clinical guidelines will be updated and swift UK-wide implementation will be possible due to the use of generic agents and standard equipment for treatment delivery. If Gem-Doce is superior to BCG we envision consequent reductions in cystectomy rates, international impact and rapid practice change worldwide.

2. TRIAL OBJECTIVES

2.1. Primary Objective

- To determine if Gem-Doce is non-inferior to BCG for HR-NMIBC in terms of high grade recurrence-free survival (hgRFS).

2.2. Secondary Objectives

- To compare recurrence-free survival, progression-free survival, cystectomy-free survival, cancer-specific survival and overall survival of Gem-Doce and BCG.
- In the subgroup of patients with carcinoma in situ at trial entry, to compare complete response rate at 6 months between Gem-Doce and BCG.
- To compare the compliance (number of instillations received), safety and tolerability of both treatments measured by clinician-reported symptoms using CTCAE v5. [22]
- To compare patient-reported health related quality of life over the 24-month maintenance visit follow-up period, measured by the generic EORTC QLQ-F17, disease specific QLQ-NMIBC24 and the generic EQ-5D-5L validated instruments. [23-25]
- To estimate quality adjusted life years (QALYs) over the 24-month maintenance visit follow-up period and extrapolated over the patient lifetime from responses to the EQ-5D-5L, cross-walked from responses to the EORTC QLQ-F17 as a sensitivity analysis.
- To estimate cost to the NHS and personal social services over the 24-month maintenance visit follow-up period and extrapolated over the patient lifetime.
- To estimate the relative cost-effectiveness of the two treatments over the 24-month maintenance visit follow-up period and extrapolated over the patient lifetime.

2.3. Exploratory Objectives

- To determine oncological outcomes of patients developing high grade recurrence following allocated treatment who then receive the alternative, non-allocated treatment (BCG allocated participants with high grade recurrence receiving Gem-Doce and vice versa).

3. TRIAL DESIGN

COBRA is a pragmatic open-label phase III multicentre randomised controlled trial. An internal pilot phase will assess recruitment related performance measures.

The target population is people with a new HR-NMIBC diagnosis receiving treatment within the NHS.

Participants will be randomised (1:1) to either:

- **Control**: standard of care BCG bladder instillations (6 once-weekly induction instillations followed by 3 once-weekly maintenance instillations at 3, 6, 12, 18 & 24 months).
- **Experimental**: Gem-Doce bladder instillations (six once-weekly induction instillations followed by once-monthly maintenance instillations from 3 to 24 months).

Participants will be followed up for 5 years in accordance with NICE guidelines.

Participants who have high grade NMIBC recurrence during follow-up will be offered the alternative, non-allocated treatment if they do not have cystectomy.

4. TRIAL ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is time to first identification of high grade recurrent disease, stage progression, metastatic disease or death from any cause.

4.2. Secondary Endpoints

- Recurrence-free survival
- Progression-free survival
- Cystectomy-free survival
- Cancer-specific survival
- Overall survival
- Complete response rate at 6 months (in patients with carcinoma in situ at baseline only)
- Number of instillations received
- Clinician assessed adverse events
- Patient-reported outcomes – health related quality of life with an emphasis on overall quality of life, physical functioning, urinary symptoms and intravesical treatment issues
- Costs to the NHS and personal social services
- Incremental cost per quality adjusted life year gained

4.3. Exploratory Endpoint

- High grade recurrence in participants who receive the alternative, non-allocated treatment after initial recurrence.

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of Participants

The aim is to recruit 520 participants; 260 into each group of the study.

5.2. Source of Participants

Participants will be recruited from approximately 50 participating sites in the UK. Potential participants may be identified via local review of medical records or in urology clinics and should be discussed at Multi-Disciplinary Team (MDT) meetings.

ICR-CTSU encourages investigators to consider equality, diversity and inclusion when recruiting participants into its trials, to ensure that everyone eligible is offered the opportunity to consider participation.

5.3. Inclusion Criteria

1. Able to provide written informed consent prior to any study-specific procedures
2. Age >=18 years
3. WHO performance status 0-3
4. A new diagnosis of high-risk urothelial NMIBC with no variant histology:

pT1 G2-3/high grade tumour (with or without CIS) ***OR***
pTa G3/high grade tumours (with or without CIS) ***OR***
Isolated carcinoma in situ (CIS)

5. Complete papillary tumour removal (apart from residual CIS) via TURBT
6. All patients with pT1 at initial TURBT should have had re-TURBT if there was no muscle in initial TURBT specimens. Re-resection should also be considered for patients with HG Ta if no muscle was present or for patients with HG T1 with muscle present at initial TURBT, according to local practice
7. Willing to use an effective method of contraception *(see section 5.5 – Lifestyle Guidelines for details)*
8. Willing and able to comply with the follow-up schedule

5.4. Exclusion Criteria

1. Any previous history of urothelial cancer
2. History of pure non-urothelial cell bladder cancer (adenocarcinoma, squamous cell carcinoma)
3. Evidence of neuroendocrine (small/ large cell) sarcomatoid, micropapillary or plasmacytoid variant urothelial cell cancer
4. Any urethral involvement
5. Any medical condition that contraindicates study treatment, including any known allergy to gemcitabine, docetaxel or BCG
6. Known pregnancy and/or currently breastfeeding
7. Known HIV, Hepatitis B or C with detectable viral load within 30 days prior to randomisation
8. Ongoing immunosuppressive medication, including steroids (>10mg/day) - people receiving short courses (two weeks maximum) of steroids due to be discontinued prior to randomisation or using inhaled and topical steroids are eligible for randomisation
9. Active or treated malignancy within 1 year of randomisation (not including non-melanomatous skin carcinoma, NICE low risk prostate cancer (T1/T2a, Gleason 6 PSA <10), in situ carcinoma of any site)

5.5. Lifestyle Guidelines

Participants who could become pregnant must agree to practice true abstinence, or use a highly effective contraceptive measure (as listed below) during the period of trial treatment and for 6 months after the last dose of trial treatment, or be surgically sterile (i.e. either have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or have a sterilised sole partner, or be post-menopausal.

If participants have sexual intercourse with someone who is, or could become, pregnant they must use a condom during trial treatment and for 6 months after the last dose of trial treatment. Partners of participants who could become pregnant should use a highly effective form of contraception (as listed below). Participants should not donate sperm throughout the period of trial treatment and for 6 months following the last dose of trial treatment. Participants considering starting a family should seek advice about the possibility of sperm preservation before starting trial treatment.

Highly effective birth control methods:

Birth control methods considered as highly effective are those which achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
    - oral

  - injectable
  - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of a participant who could become pregnant, and that the vasectomised partner has received medical confirmation of the vasectomy's success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method if refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence should be evaluated in relation to the duration of the period of risk and the preferred and usual lifestyle of the participant.

6. SCREENING

6.1. Screening Log

All participating sites will be required to keep a log of all patients with a new diagnosis of HR-NMIBC who are planned for BCG treatment as part of the local care pathway. These patients are potentially eligible for this study. The information collected on the log will include:

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

No patient identifiable data should be submitted to ICR-CTSU on screening logs. Information provided will be used by the Trial Management Group to monitor recruitment activity.

6.2. Procedure for Obtaining Informed Consent

The Principal Investigator (or designated individual) must ensure that each participant is fully informed about the nature and objectives of the trial and possible risks associated with participation. Participants should be given the current ethics approved COBRA patient information sheet for their consideration. Information giving should be tailored to the needs of the potential participant, and the patient information sheet may be provided in a layered approach, using the separate sections noted in the document's header. Patients should only be asked to consent to the study after they have received the whole patient information sheet, had sufficient time to consider the trial, and the opportunity to ask any further questions.

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

Patients who consent to COBRA will be asked to consent to complete quality of life questionnaires. Patients should be made aware that the completion of questionnaires is entirely voluntary. Refusal to complete questionnaires will not result in ineligibility to participate in the clinical trial and will not impact the medical care received.

Patients who consent to COBRA will be asked to consent to donate tissue for future research. Routinely obtained and stored tissue taken for diagnosis will be collected for the translational sample collection. Collection of tissue is entirely voluntary and refusal to donate diagnostic tissue will not result in ineligibility to participate in the clinical trial and will not impact the medical care received.

Confirmation of the participant's consent and the informed consent process must be documented in their medical records. A copy of the signed consent form should be provided to the participant 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 Research

COBRA participants will not be permitted to participate in any other trials of investigational medicinal products whilst they are being treated within COBRA or for 4 months afterwards. Participation in other clinical trials will be considered on a case by case basis by the Trial Management Group.

Participation in non-interventional research is permitted.

7. RANDOMISATION

Participants must have had diagnostic surgery (TURBT/second TURBT as indicated) and histological confirmation of HR-NMIBC prior to randomisation.

Randomisation and treatment allocation will be conducted by site staff via the trial database.

Randomisation and commencement of intravesical treatment should take place within 8 weeks following definitive TURBT.

An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required:

- Name of hospital, consultant and person randomising the participant
- Confirmation that the participant has given written informed consent for trial
- Confirmation that the participant is eligible for the trial following local completion of the eligibility checklist
- Participant's full name, hospital number, date of birth, postcode and NHS/CHI number
- Date of initial TURBT
- Date of re-TURBT (if performed/ indicated)
- Planned start date of COBRA treatment
- Whether participant has consented to:
    - Complete quality of life questionnaires
    - Donate diagnostic tissue for future research
    - Permit linkage to routine healthcare data held by NHS England
    - Future sharing of deidentified clinical data for future research

Participants should be informed of their treatment allocation, and provided with the relevant treatment guidance document, following randomisation.

8. TRIAL ASSESSMENTS

8.1. Screening Assessments

The following assessments should be conducted within 8 weeks prior to randomisation for all participants unless otherwise stated:

- Physical examination
- Vital signs assessment

- ECOG performance status
- Safety bloods: Haematology and Biochemistry (within 3 months prior to randomisation).
- Upper urinary tract imaging (ultrasound / CT according to local practice <6 months from diagnosis)
- Completion of patient reported questionnaire booklet (EORTC QLQ-F17, QLQ-NMIBC24, EQ-5D-5L), if participating.
- Possibility of pregnancy should be verified verbally with each participant prior to randomisation, with testing as clinically indicated in accordance with local standard practice.

8.2. Pre-induction Assessments

The following assessments should be conducted within 14 days prior to starting COBRA induction treatment:

- Pregnancy test (urine/blood) for participants who could become pregnant
- Symptom assessment (CTCAE V5) [22]

8.3. Induction Assessments (both treatment groups)

Induction BCG and Gem-Doce treatments should be given as detailed in section 9 and should take place within 8 weeks following last TURBT (initial TURBT or re-TURBT where applicable).

The following assessments should be conducted prior to each induction treatment instillation for all participants:

- Urine dipstick UTI test (BCG group only)
- Symptom assessment (CTCAE V5) [22]
- Pregnancy test (urine/blood) for participants who could become pregnant (at induction week 4 only)

8.4. Maintenance Visit Follow-up

BCG and Gem-Doce treatments should be given as detailed in section 9 and should take place within 3 weeks following check cystoscopy. Where a TURBT/ GA bladder biopsy is performed for a suspicion of recurrence, intravesical treatment should take place within 6 weeks.

8.4.1. Maintenance Follow-up Assessments

- Cystoscopy (flexible/rigid, according to local practice, at 3m, 6m, 9m, 12m, 15m, 18m, 21m and 24m), with biopsy of any suspicious areas of bladder urothelium (papillary or red patches suspicious for CIS) prior to any fulguration.
- Upper urinary tract imaging (according to local practice at 12m and 24m visit only. Contrast CT recommended but ultrasound or non-contrast CT permitted for participants with impaired renal function).
- Urine dipstick UTI test prior to each instillation (BCG group only)
- Physical examination at 3m, 12m and 24m.
- Vital signs assessment at 3m, 12m and 24m.
- Safety bloods: Haematology and Biochemistry at 3m, 12m and 24m.
- Symptom assessment (CTCAE V5 [22]) at 3m, 6m, 9m, 12m, 15m, 18m, 21m and 24m.
- Completion of patient reported outcomes questionnaire (EORTC QLQ-F17, QLQ-NMIBC24, EQ-5D-5L, health service usage), if participating.
  3m questionnaires should be provided to participants by sites. 6m-24m questionnaires are provided directly to participants by ICR-CTSU.
  - Patient reported outcomes at 3m, 6m, 12m, 18m and 24m.
  - Health service usage at 6m, 12m, 18m and 24m.

- All participants will be asked to complete a demographic survey (DISTINCT), which will be provided to them directly by ICR-CTSU following trial entry.
- Pregnancy test (urine/blood) for participants who could become pregnant after final treatment instillation.

8.5. Post Maintenance Follow-up

Follow up should continue six monthly in years 3 to 4 and annually thereafter in accordance with NICE guidelines. Follow up may include flexible or rigid cystoscopy according to local practice.

8.6. Procedure at Disease Progression/Recurrence

See Appendix A4 for flowchart of required procedures.

8.6.1 At Any Time Point

Where there is a clinical suspicion of recurrence observed on cystoscopy, a TURBT/ bladder biopsy is mandated prior to fulguration. Any areas suspicious for CIS (ie: red patches) should be biopsied.

8.6.2 Three Month Cystoscopy After Induction Therapy

Histological confirmation of LG/G1-2 Ta or CIS

- Continue with first maintenance course of allocated treatment as planned and continue follow up per protocol.

Histological confirmation of HG/G3 Ta disease

- The non-allocated treatment should be offered (see section 9.2).

Histological confirmation of HG/G2-3 T1 disease

- Participants should be offered radical cystectomy, if considered a suitable treatment option according to local clinical judgement.
- If cystectomy is considered unsuitable or declined the non-allocated treatment should be offered (see section 9.2).
- Participants who decline radical cystectomy and the non-allocated treatment should be treated according to local clinical judgement.
- Participants should continue to be followed-up for secondary endpoints related to disease progression and survival.

Histological confirmation of MIBC

- Participants should be treated according to local clinical judgement.
- Participants should continue to be followed-up for secondary endpoints related to survival.

8.6.3 Six Month Cystoscopy After Induction Therapy and Beyond

Histological confirmation of LG/G1-2 Ta disease

- Participants should proceed with the remaining maintenance course of their allocated treatment and continue follow up per protocol.

Histological confirmation of persistent isolated CIS or CIS with HG/G3 Ta disease or HG/G3 Ta disease

- Non-allocated treatment should be offered (see section 9.2).
- Participants who decline the non-allocated treatment should be treated according to local clinical judgement.

- Participants should continue to be followed-up for secondary endpoints related to disease progression and survival.

Histological confirmation of HG/G2-3 T1 disease

- Participants should be offered radical cystectomy, if considered a suitable treatment option according to local clinical judgement.
- If cystectomy is considered unsuitable or declined the non-allocated treatment should be offered (see section 9.2).
- Participants who decline radical cystectomy and the non-allocated treatment should be treated according to local clinical judgement.
- Participants should continue to be followed-up for secondary endpoints related to disease progression and survival.

Histological confirmation of MIBC

- Participants should be treated according to local clinical judgement.
- Participants should continue to be followed-up for secondary endpoints related to survival.

8.7. Treatment Discontinuation

Participants may discontinue from trial treatment (induction or maintenance) at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease progression or recurrence
- Unacceptable toxicity
- Pregnancy
- Need for radical cystectomy in opinion of treating clinician

Participants who discontinue treatment should continue to be followed up per protocol and the following assessments should be conducted:

- Physical examination
- Vital signs assessment
- Safety bloods: Haematology and Biochemistry.
- A pregnancy test should be conducted at treatment discontinuation for participants who could become pregnant.

8.8. Changes in Participation Status

Participants may choose to change, reduce or stop their participation after joining the trial.

Within COBRA the following changes in participation are possible:

- Stopping trial specific follow up – data will continue to be requested from routine visits.
- Stopping routine clinical follow up – data will continue to be requested from details in the participants' medical record (e.g. date of progression/death).
- Stopping participation in patient reported outcomes or tissue collection studies.
- Stopping donated samples being used in COBRA research/analysis
- Stopping future sharing of data.
- Stopping future sharing of samples.
- Withdrawal of consent for any further data to be submitted – data up to the point of withdrawal will be retained as described in the patient information sheet.

Any other requested changes should be discussed on a case-by-case basis with ICR-CTSU.

Changes in participation should be led by the participant and no assumptions should be made on their behalf. A change in participation status form should be submitted to ICR-CTSU to report the details of any reduction in participation. For further guidance on the types of change in participation status and guidance on loss of contact, please refer to trial guidance notes.

8.9. Schedule of Assessments

	Pre-randomisation*	Induction						Maintenance									Follow up				
		BCG / Gem-Doce						Gem-Doce	BCG								Both groups				
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Monthly 3m – 24m	3m	6m	9m	12m	15m	18m	21m	24m	30m	36m	42m	48m	60m
Written informed consent	x																				
Confirmation of eligibility	x																				
Medical history	x																				
Physical examination	x							x[7,8]	x			x				x[8]					
Vital signs	x							x[7,8]	x			x				x[8]					
Haematology and biochemistry[Π]	x							x[7,8]	x			x				x[8]					
ECOG PS	x																				
Upper urinary tract imaging[€]	x							x[1]				x				x					
Pregnancy test if applicable	x				x			x[8]								x[8]					
Treatment delivery		x	x	x	x	x	x	x	x[2]	x[2]		x[2]		x[2]		x[2]					
Urine dipstick[α]		x	x	x	x	x	x		x[2]	x[2]		x[2]		x[2]		x[2]					
Cystoscopy (flexible/rigid)								x[3]	x	x	x	x	x	x	x	x	x	x	x	x	x
Biopsy of any site of recurrence[¥]								x[3]	x	x	x	x	x	x	x	x	x	x	x	x	x
Assessment of symptoms/toxicity	x	x	x	x	x	x	x	x[3]	x	x	x	x	x	x	x	x					
Health service usage								x[5]		x		x		x		x					
Quality of life questionnaire	x							x[4, 6]	x[4]	x		x		x		x					

Footnotes:

* Within 8 weeks prior to randomisation

Π Within 3 months prior to randomisation

€ Ultrasound / CT according to local clinical practice <6 months from diagnosis

¥ Any suspicious areas of bladder urothelium should be biopsied prior to any fulguration. Formalin-fixed paraffin embedded blocks of confirmed recurrent disease will be centrally collected.

α For BCG group only.

1. At 12m, 24m
2. 3 once weekly instillations per timepoint
3. At 3m, 6m, 9m, 12m, 15m, 18m, 21m, 24m
4. Administered by site to 3m only
5. At 6m, 12m, 18m, 24m
6. At 3m, 6m, 12m, 18m, 24m
7. At 3m, 12m
8. At 24m or end of treatment (if earlier).

9. TRIAL TREATMENT

The generic agents Bacillus Calmette-Guérin (BCG), gemcitabine and docetaxel are the investigational medicinal products for intravesical delivery within COBRA.

9.1. Dose and Schedule

Participants should be recommended to restrict fluid intake for 4 hours prior to treatment.

9.1.1. BCG Dose and Schedule

BCG should be delivered in accordance with local practice and manufacturers guidance unless otherwise specified below. Any BCG licensed for intravesical use in the UK can be administered. Urinary tract infection should be excluded prior to each instillation.

Six once-weekly induction instillations of intravesical BCG (one dose per instillation as per standard of care using local hospital stock, in 50ml sodium chloride 0.9%), delivered via catheter under local anaesthetic lubricating jelly, followed by maintenance therapy. Refer to local pharmacy policy and the summary of product characteristics for the local standard BCG product for further details of dosing requirements.

BCG maintenance should be delivered in three once-weekly instillations at months 3, 6, 12, 18 and 24 (15 instillations).

Participants should aim to have a drug dwell time of at least 60 minutes and up to 120 minutes and may be discharged immediately following instillation of BCG.

9.1.2. Gem-Doce Dose and Schedule

Six once-weekly induction intravesical instillations, delivered via catheter under local anaesthetic lubricating jelly, followed by maintenance therapy.

Gem-Doce maintenance should be given as once-monthly intravesical instillations from month 3 to month 24 (22 instillations).

It is recommended that patients randomised to Gem-Doce should be prescribed 1g of sodium bicarbonate to take the evening before and the morning of treatment.

9.1.3. Gemcitabine

Participants should receive gemcitabine (1g in 50ml sodium chloride 0.9%, ensuring the final concentration is within stability range limits as specified within the summary of product characteristics for the local hospital stock and local pharmacy policy) instilled over five minutes, and the catheter should be clamped for at least 60 minutes, during which time participants should remain in clinic.

9.1.4. Docetaxel

Following drainage of gemcitabine, docetaxel (40mg in 60ml sodium chloride 0.9%, ensuring the final concentration is within stability range limits as specified within the summary of product characteristics for the local hospital stock and local pharmacy policy) should be instilled, after which the catheter can be removed and patients may be discharged.

Participants should aim to have a drug dwell time of at least 60 minutes and up to 120 minutes.

9.2. Participants Switching to Non-Allocated Treatment Group

Participants may be offered the non-allocated treatment following high grade recurrence (section 8.6) at any point after randomisation. In this circumstance, it is recommended that induction and maintenance schedules detailed above are used as a guide to treatment delivery.

9.3. Prescription and Dispensing

Both BCG and Gem-Doce are generic investigational medicinal product(s) within COBRA and should be prescribed by the local investigator and dispensed from hospital pharmacy from hospital stock for the duration of the trial. BCG is being used within its licensed indication. Whilst gemcitabine and docetaxel have a marketing authorisation, within COBRA these products are being used off-label. Any available brand of each IMP may be used, providing dosing guidance above is adhered to.

9.4. Patient Cards

Small wallet sized cards will be produced by ICR-CTSU on request by the participating site. Each card will state:

- the name of the participating site
- that the patient is participating in the COBRA trial
- that the patient is receiving BCG or Gem-Doce
- an emergency contact number

9.5. Duration of Treatment

In both groups participants will receive six once-weekly induction instillations delivered via catheter under local anaesthetic. Maintenance therapy should continue until 24 months from the start of induction treatment according to the schedules detailed above (section 9.1).

9.6. Supportive Care and Dose Modifications

For participants with bladder spams or who have difficulty retaining intravesical therapy, anticholinergics/ beta-3-agonists are recommended to be given 2 hours before intravesical drug instillation. Antiemetics such as ondansetron taken prophylactically are permitted at the discretion of the treating physician.

9.6.1. Toxicity management recommendations

Adverse Event	**BCG**	**Gem-Doce**
Transient symptoms; urinary frequency, urgency, dysuria, cystitis, malaise, fever < 38.0 ° C	Continue intravesical BCG treatment. Expected after intravesical BCG and usually resolves within 48 hours. If urinary symptoms persist, consider delaying treatment till symptoms resolve/ improve. Consider symptomatic treatment (anticholinergics/ beta 3 agonist). Consider urine culture. If symptoms persist consider reducing dose level in accordance with section 9.6.2. Dose reduction is recommended before decision to stop therapy. If symptoms improve, consider titrating dose up.	Continue intravesical Gem-Doce treatment. Expected after intravesical Gem-Doce and usually resolves within 48 hours. If urinary symptoms persist, consider delaying treatment till symptoms resolve/ improve. Consider symptomatic treatment (anticholinergics/ beta 3 agonist). Consider urine culture.
Persistent (> 48 hour) fever < 38.0° C, cystitis, malaise	Hold BCG until symptoms subside.	Hold Gem-Doce until symptoms subside.

Adverse Event	BCG	Gem-Doce
	Order urine culture and consider antibiotics based on culture sensitivities. Resume treatment at the same dose level. If symptoms persist consider reducing dose level in accordance with section 9.6.2.	Order urine culture and consider antibiotics based on culture sensitivities. Resume treatment at the same dose level.
Fever > 38.0°C for 12-24 hours	Hold BCG until symptoms subside. Order urine culture and start antibiotics; consult infectious diseases clinician and treat as per local clinical standard. Resume intravesical BCG at the same dose level when asymptomatic.	Hold Gem-Doce until symptoms subside. Order urine culture and start antibiotics; consult infectious diseases clinician if needed.
Acute severe illness, local or systemic pneumonitis, hepatitis, prostatitis, urethral obstruction, renal abscess, persisting high fever > 39° C	Consider permanently discontinuing intravesical BCG. Consult infectious diseases clinician and treat as per local clinical standard.	Consider permanently discontinuing intravesical Gem-Doce. Consult infectious diseases clinician and treat as per local clinical standard.
Sepsis	Consider permanently discontinuing intravesical BCG. Consult infectious diseases clinician.	Unlikely to occur, however if present, consider permanently discontinuing Gem-Doce. Consult infectious diseases clinician.
Allergic reaction	Rash may be treated with topical steroid creams or antihistamines. If they persist, consider referral to dermatology. Patients who develop anaphylaxis, difficulty breathing, wheezing, generalized oedema should be treated as per advanced life support protocols and permanently discontinue BCG.	Unlikely to occur, however if present, rash may be treated with topical steroid creams or antihistamines. If they persist, consider referral to dermatology. Patients who develop anaphylaxis, difficulty breathing, wheezing, generalized oedema should be treated as per advanced life support protocols and permanently discontinue Gem-Doce.

All adverse events and any changes to treatment delivery should be reported on the appropriate pages of the CRF.

9.6.2. BCG Dose Modifications

Dose modifications are permitted to manage BCG related toxicities and increase likelihood of completion of therapy. Dose modifications should be as follows:

Full Dose	Reduce dose 1	Reduce dose 2	Reduce dose 3
One dose per instillation	1/3 dose	1/4 dose	1/10 dose

Any modifications to BCG doses should be reported on the appropriate pages of the CRF.

9.6.3. Gem-Doce Dose Modifications

No dose modifications are permitted in the Gem-Doce group (see section 9.9).

9.7. Concomitant Therapy

All medication considered necessary for the participants' welfare and not expected to interfere with 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. Low dose corticosteroid use is permitted.

9.8. Non-permissible Medications/Therapies

Non-permissible concurrent medications/therapies include:

- Systemic chemotherapy
- Systemic immunotherapy
- High dose corticosteroids (equivalent to prednisolone >10mg/day)
- Any investigational medicinal product (for any indication)
- Any live vaccine

9.9. Dose Delays

Instillations should not be given within 3 weeks following TURBT, GA bladder biopsy. In patients who had a traumatic catheterisation, acute urinary tract infection or bladder perforation, intravesical instillation should be delayed until after recovery.

9.9.1. Induction

The six week induction treatment schedule should be completed in a maximum of nine weeks for both treatment groups.

9.9.2. Maintenance

For BCG maintenance therapy, the planned 3 weekly instillations should be completed within a maximum of 6 weeks.

For Gem-Doce maintenance therapy, the instillations should be completed within 3 weeks.

9.10. BCG Shortage

Should shortages of BCG supply arise during the trial, the dose may be modified to provide participants a minimum of one-third dose BCG instead of the full dose to maximise patient access across the UK (section 9.6.2). Generic agents are being used in the trial and any BCG strains approved by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) in future will be permitted in COBRA to maximise BCG availability.

9.11. Discontinuation and Subsequent Therapy

Participants may discontinue from trial treatment (induction and maintenance) at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator (section 8.7). Subsequent therapy should be given according to local clinical judgement. Follow up should continue per protocol.

9.12. Provision of Treatment Beyond the End of the Trial

There are no plans to provide trial treatment beyond the end of the trial. Patients will revert to standard of care.

9.13. Labelling and Pharmacy Responsibilities

At the time of dispensing it is the responsibility of the site to comply with Annex 13 labelling requirements for the final formulation prior to administration. Drug formulation, storage, accountability and destruction should be in accordance with local policy. ICR-CTSU should be provided with confirmation of the local pharmacy's procedures prior to site activation.

10. PHARMACOVIGILANCE

10.1. Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered an investigational medicinal product; the event does not necessarily have a causal relationship with the treatment or usage.

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- 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, death due to progression of the indicated disease and planned hospital admissions (e.g. for surgery) are not considered SAEs and do not need to be reported as such but should be reported on the appropriate CRF.

Pregnancy or aid in the conception of a child whilst participating in a trial is not considered an SAE but should be followed up for congenital anomalies or birth defects (see section 10.8).

SAE Reporting Period

SAEs that occur after randomisation and within 30 days of the last administration of trial treatment (i.e. completion of 24-month maintenance therapy).

Any SAEs that occur after the SAE reporting period that, in the opinion of the Principal Investigator, are related to the study drug should be reported to ICR-CTSU if the Principal Investigator becomes aware of them.

Serious Adverse Reaction (SAR)

A serious adverse reaction is an SAE that is suspected as having a causal relationship to the investigational medicinal product, 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 drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the information set out in the Reference Safety Information (RSI).

10.1.1. Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

For BCG treatment, the RSI for the COBRA Trial is contained in Section 4.8 of the representative Summary of Product Characteristics (SmPC) provided. Available SmPCs for gemcitabine and docetaxel are for intravenous delivery only. Administration in this trial is intravesical and therefore use of Section 4.8 of the gemcitabine and docetaxel SmPCs as RSI is not considered appropriate.

Only the following known side-effects of intravesical gem-doce delivery will be considered expected for the purposes of SAR assessment in COBRA:

- Haematuria
- Urinary tract infection
- Urinary tract pain

Fatal or life-threatening serious adverse reactions listed above will be considered unexpected and subject to expedited regulatory reporting.

10.2. Reporting Adverse Events to ICR-CTSU

Any toxicity, sign or symptom that occurs within the reporting period defined above, which is not unequivocally due to progression of disease, should be considered an AE. Out of range laboratory values should only be reported as AEs if they are clinically relevant (i.e. indicative of a clinical sign or

symptom). The sign/symptom should be reported as the AE and the associated laboratory value provided as additional information where relevant.

All treatment related AEs must be reported on the relevant CRF as applicable.

The severity of AEs should be graded according to the NCI CTCAE criteria version v5.0. [22] For each AE, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/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 within the SAE reporting period defined above must be reported.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the COBRA SAE form in the trial database.

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 and electronically signed and dated by the Principal Investigator or designated representative.

10.4. Review of Serious Adverse Events

All reported SAEs will be reviewed by the Independent Data Monitoring Committee.

The Chief Investigator (or designated representative) will assess all SAEs reported as related to the randomised trial treatment, i.e. BCG, gemcitabine or docetaxel, for causality and expectedness. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality.

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 10.5).

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, the Sponsor, and all other interested parties 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 Sponsor within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA and the Sponsor 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 appropriate intervals.

10.6. Follow up of Serious Adverse Events

The Principal Investigator should actively seek follow up information on reported SAEs. 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 or designee becomes aware of the outcome.

10.7. Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA by ICR-CTSU and copied to the Sponsor at the end of the reporting year.

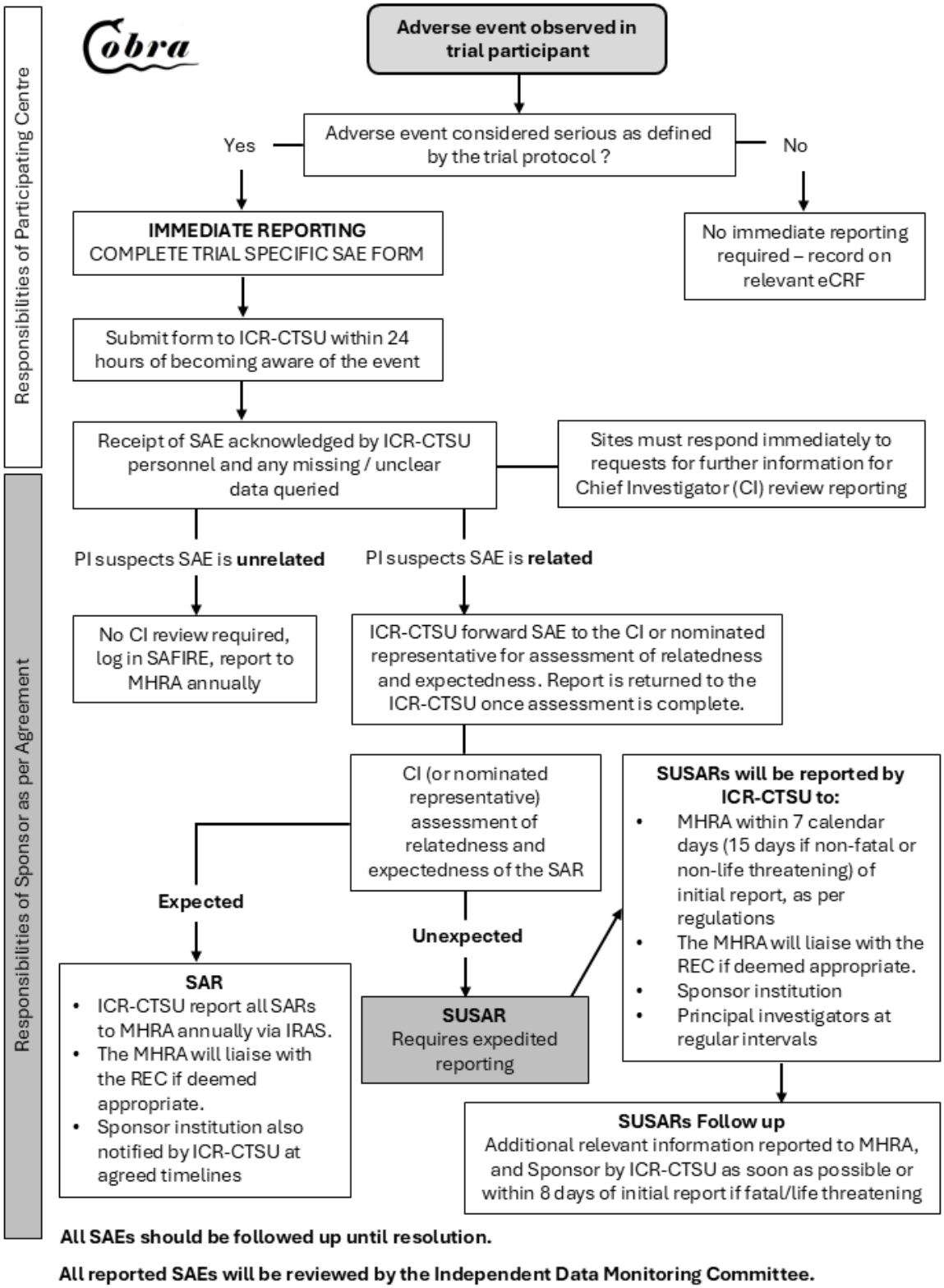
10.8. Reporting Pregnancies

If any trial participant or a trial participants' partner becomes pregnant while receiving study drug or up to 30 days after receiving study drug, this should be reported to ICR-CTSU using the pregnancy reporting CRF. 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.

10.9. Urgent Safety Measures

Any urgent safety measures that may arise during the trial will be reported by the ICR-CTSU to the MHRA within required timelines in accordance with current regulations and guidance.

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



11. STATISTICAL CONSIDERATIONS

11.1. Statistical Design and Sample Size Justification

COBRA is a pragmatic open-label phase III multicentre RCT with the primary objective of evaluating if Gem-Doce is non-inferior to BCG for HR-NMIBC and is cost-effective (see section 12 for Economic considerations).

The non-inferiority design was chosen following discussions with patient and public involvement (PPI) advisors and co-investigators. COBRA tests the hypothesis that Gem-Doce is non-inferior in terms of high grade recurrence-free survival (hgRFS) and better tolerated with fewer side effects than BCG. Whilst a superior treatment to BCG would be ideal, the only current data reporting superiority of Gem-Doce (24-month hgRFS 81% vs 69%, hazard ratio =0.57, 95% CI: 0.33-0.97, p=0.04) comes from a retrospective study which had limitations in terms of the BCG maintenance regimen which could have compromised its efficacy.[26] We have published retrospective data in intermediate risk NMIBC which suggested similar outcomes between BCG and Gem-Doce (HR=0.88, 95% CI 0.47-1.64; p=0.7).[27] While good cancer outcomes are essential to support introduction of a new treatment within the NHS, our PPI advisors highlighted that adverse events following BCG and issues with treatment tolerability, which can lead to cessation of BCG prior to completing a full course, are also important issues. Retrospective data suggest that induction treatment discontinuation was lower with Gem-Doce than BCG (2.9% vs 9.2%, p=0.02) with low levels of major adverse events (Gem-Doce: 1.4%, BCG: 4.0%).[11] A cost-effective non-inferior treatment with fewer adverse events and better tolerability would be welcomed by patients and clinicians alike and would change clinical practice.

The trial has a non-inferiority parallel group design. The primary outcome measure is hgRFS. The 2-year hgRFS is assumed to be 77.5% with BCG (unpublished data from the subgroup of PHOTO trial participants with high risk disease). Based on discussion with PPI advisors and clinical opinion a non-inferiority margin of 10% at 2 years was determined as the largest acceptable absolute difference in hgRFS between Gem-Doce (experimental group) and BCG (active comparator). For statistical efficiency, and to protect against deviations from the absolute control arm event rate assumption, a relative non-inferiority margin - a critical hazard ratio of 1.542 - has been utilised. In defining this non-inferiority margin, the trade-off between efficacy loss and tolerability, compliance and side-effect/health-related quality of life gains, the feasibility of achieving the target sample size, and consequent timelines for study completion were considered.

The sample size was calculated using STATA artsurv software based on the following design parameters and assumptions:

- 1:1 allocation ratio
- 4 years of staggered recruitment (15%, 25%, 30% and 30% accrued in years 1 to 4 respectively)
- 2-years minimum follow-up
- 90% power
- 5% one-sided alpha
- Critical hazard ratio of 1.542 (approximately equivalent to an absolute 10% non-inferiority margin at 2 years)
- 5% drop-out rate at the point of analysis (based on our experience in the PHOTO trial [28])

In order to achieve 90% power, a total of 185 events are needed and we anticipate that this will be achieved through recruitment of **520 patients** (494 patients with no drop-out), followed up for a minimum of 2 years.

In a secondary analysis, and to provide supporting evidence for wider stakeholder confidence in the non-inferiority margin, historical control data from 219 evaluable patients recruited to PHOTO will be incorporated in a Bayesian framework. Accounting for between-study heterogeneity, these data will

be down-weighted to give an equivalent prior effective sample size (ESS) of 110 – 202. Specifically, the historical data can be translated into an expected local-information-ratio ESS[29] of:

- 202 on the control, assuming highly commensurate historical and contemporary control data, which is equivalent to a Generalised-Gamma(a=13.7, s=1, f=14.8) prior, *or*
- 110 on the control, assuming moderately commensurate historical and contemporary control data, which is equivalent to a Generalised-Gamma (a=10.0, s=1, f=11.1) prior

for the hazard parameter of the exponentially distributed control data.

A vague prior will be placed on the parameter that underpins the treatment group data. This method warrants a basic predictive consistency criterion, that is, the expected posterior predictive ESS for a new control group of size n_C equals the sum of the prior ESS and n_C. Thus, assuming historical controls are highly [moderately] commensurate with the observed data leads to the comparison of 247 patients on Gem-Doce and 449 [357] equivalent patients on BCG. Controlling for a (Bayesian analogue of) type 1 error rate at approximately 5%, our simulations suggest that the analysis can achieve 81.3% [77.1%] power to detect the difference setting a 2-year non-inferiority margin of 7.5% (critical hazard ratio 1.40). Code for the calculations using historical control data is available on GitHub.[30]

The design will permit testing for superiority of Gem-Doce if non-inferiority is observed.

11.2. Treatment Allocation

Participants will be randomised to receive either BCG or Gem-Doce on a 1:1 basis.

Treatment allocation is by computer generated random permuted blocks. Randomisation will be stratified by randomising centre and presence of carcinoma in situ (yes/no).

11.3. Endpoint Definitions

Time to event endpoints will be measured in days from date of randomisation unless otherwise stated.

11.3.1. Primary Endpoint

HgRFS: time to earliest date of identification of high grade recurrent disease (including disease progression), metastatic disease or death from any cause. Persistent/recurrent HG pT1 or HG Ta papillary bladder cancer following induction therapy or persistent carcinoma in situ at 6 months will be considered high grade recurrence events. The development of nodal disease or distant metastatic disease (based on cross-sectional imaging or histological confirmation - where biopsy is done, histology results will supersede imaging) is considered a high grade recurrence event. For participants with no recorded event, hgRFS will be censored at the date of last follow-up when they were free of high grade disease.

11.3.2. Secondary Endpoints

RFS: as for hgRFS but includes recurrences of any grade as events.

Progression-free survival: time to the earliest date of identification of disease progression or date of death from any cause. Progression is defined as tumour stage ≥pT2 at TURBT (i.e. muscle-invasive disease) or the development of nodal disease or distant metastatic disease (based on cross-sectional imaging or histological confirmation - where biopsy is done, histology results will supersede imaging).

Cystectomy-free survival: time to the date of radical cystectomy or death from any cause.

Cancer-specific survival/overall survival: time to date of death from bladder cancer / any cause respectively.

Complete response rate at 6 months: absence of cancer at 6 month cystoscopy (in patients with carcinoma in situ at baseline only).

Number of instillations received: total number of instillations received during the allocated therapy.

Clinician assessed adverse events: assessed using CTCAE v5.0.[22]

Health related quality of life: see Appendix A1.

Health economics, costs to the NHS and personal social services, cost-effectiveness: see section 12.

11.3.3. Exploratory Endpoints

HgRFS following receipt of non-allocated treatment: As for hgRFS for participants who receive the alternative, non-allocated treatment following a first high grade recurrence (section 9.2). Time will be measured from start of the alternative, non-allocated treatment.

11.4. Statistical Analysis Plan

Statistical analyses of all endpoints other than health economic related will be conducted at the ICR-CTSU. The secondary analysis under a Bayesian framework will be conducted in collaboration with Dr H Zheng (University of Bath). Analysis details are outlined here in brief. Full details will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures. Health economics analysis and evaluation is detailed in section 12.

The primary analysis of hgRFS is planned to take place once the target number of events has been observed which is expected to be when participants have at least 2 years follow up (and will have completed study treatment). The Independent Data Monitoring Committee (IDMC) will monitor the accumulation of follow-up data and primary endpoint events in the trial and will advise on when the dataset is sufficiently mature for analysis; analysis prior to the target number of events would need to be sufficiently robust to have potential to influence clinical practice. Unless advised otherwise by the IDMC, secondary endpoints will be reported at the time of the primary analysis. In addition, there will be subsequent analyses of all endpoints which will use data from longer follow-up periods.

Efficacy analyses, including the analysis of the primary endpoint, will include all randomised participants according to allocated treatment arm (intention-to-treat). As this is a non-inferiority trial, a sensitivity analysis of the primary endpoint will be conducted in the per protocol population comprising randomised participants who completed at least 5 out of 6 induction instillations of allocated treatment, plus 2 out of the first 3 maintenance instillations of allocated treatment (for BCG this is 2 out of the first 3 weekly instillations at month 3 and for Gem-Doce this is 2 out of the first three instillations out of months 3, 4 and 5). In addition, a pre-planned analysis will also be conducted in participants who have 5 out of 6 induction doses plus at least 50% of maintenance doses of allocated treatment (this corresponds to a minimum of 8 maintenance instillations of BCG, and 11 maintenance instillations for Gem-Doce). However, we will not require a “positive” result in this population to claim non-inferiority.

Analysis of toxicity and quality of life endpoints will be in the safety population of all randomised patients who received at least one instillation of study treatment.

Baseline characteristics will be reported by allocated treatment.

Primary endpoint: analyses will estimate the size of the treatment effect with a 90% confidence interval for the estimated difference between randomisation groups (equivalent to one-sided 95% confidence interval). Information will be provided on both the absolute and relative treatment effects. Estimates of event rates will be calculated using the Kaplan-Meier method. Non-inferiority of Gem-Doce versus BCG will be tested with the log-rank test using the critical hazard ratio of 1.542 used for the sample size calculation with $p<0.05$ deemed statistically significant. Cox proportional hazards models will be used to adjust for stratification factors and additionally for important known prognostic factors. Proportional hazards assumptions will be checked and, if violated, appropriate alternative methods will be applied. Patients alive and free of event at the time of analysis and patients lost to

follow-up will be censored at the data of last assessment of disease. The primary time-point of interest is 2 years.

The use of cumulative incidence curves for time to recurrence/progression will also be explored. Recurrence free survival will be tested for non-inferiority, and if non-inferiority is demonstrated also for superiority. All other endpoints will be tested for superiority.

In the subgroup of patients with CIS at trial entry, the proportion of patients with a complete response at the 6 month assessment will be compared using a chi-squared test, with $p<0.05$ considered statistically significant.

Summary statistics on the number of instillations, time on maintenance treatment and proportion of planned instillations received will be reported and compared between treatment groups. A chi-square based test will be used to compare the proportion of patients receiving 90% or more of the protocol specified dose.

Frequencies of adverse events (overall (i.e. any grade), and by grade) will be tabulated at each timepoint, over the on-treatment period, and overall with graphical displays used to depict trends over time. Particular focus will be given to grade 3 or higher events. Comparisons will be made using chi-square or Fisher's exact test if data are sparse.

For analysis of health related quality of life endpoints see Appendix A1.

Data from the trial may be used for analyses related to trial conduct or statistical methodology projects.

11.5. Interim Analyses and Stopping Rules

Given the non-inferiority hypothesis for the primary outcome, there will be limited value in considering interim analysis for early declaration of non-inferiority. Primary outcome data will, however, be monitored throughout the trial by the IDMC as part of their regular reviews of unmasked accumulating data and a pre-specified primary endpoint superiority monitoring guideline will be developed with their independent input.

An internal pilot will assess progression against three key performance indicators: centre set-up, recruitment rate and overall recruitment during the first 18 months after recruitment starts.

Progression criteria	**Red**	**Amber**	**Green**
Recruitment rate (patients/site/month)	<0.15 *<50% of required rate*	0.15 – 0.3 *50-100% of required rate*	>0.3 *100% of required rate*
Number of sites opened within the first 18 months	<13 *<50% of 18m target*	13 – 25 *50-100% of 18m target*	>25 *100% of 18m target*
Total number of participants within the first 18 months	<43 *<50% of 18m target*	43 – 86 *50-100% of18m target*	>86 *100% of 18m target*

Progress against targets will be reviewed monthly by the ICR-CTSU trial team and Chief Investigator throughout the 18-month pilot. Targets will also be monitored by the funder, the IDMC and independent Trial Steering Committee regularly during this period. The trial will continue to seamlessly recruit during the assessment of the 18-month pilot phase, to prevent any loss of momentum at participating sites.

12. HEALTH ECONOMIC ASSESSMENT

12.1. Data Collection

Data on use of health and care services will be collected via a service use questionnaire included in the patient reported outcomes questionnaire at 6, 12, 18 and 24 months and via CRFs completed by participating sites (section 8). Quality of life and health state utilities will be collected via the EORTC QLQ-F17 and EQ-5D-5L. Use of services will be costed from routine data sources.[31,32]

We will seek to capture all relevant costs associated with the alternative intravesical regimens and subsequent management (including adverse events) that occur during the trial follow-up. The service usage questionnaire will capture the frequency of use of health services, time away from usual activities and any privately purchased health care. Data on the time and travel costs of accessing health care will not be directly collected. These will come from previous NIHR funded studies where these have been collected and inflated to the current price year to reduce response burden for participants.[32]

12.2. Data Analysis and Modelling

A model-based cost-utility analysis from an NHS and personal social services perspective will be conducted. Trial data will be combined with other data required to model outcomes beyond that collected as part of the trial itself and will be systematically assembled from the literature. We anticipate utilising a Markov model to compare treatments, with additional regimens defined following consultation with patients and clinicians. Model structure will be informed by observed care and the lived experience of PPI advisors and the study team as well as previous models of bladder cancer treatment. The model as it is developed will be checked with these same experts to ensure consistency with their understanding of the processes modelled. We will also check whether model outputs (costs, QALYs, clinical and other outputs of relevance to our experts) are consistent with their knowledge and expectations. This process will be completed within the first 12 months of the study to facilitate the value of information analysis,[33] which will be completed alongside the internal pilot.

Cost and utility data will be analysed using appropriate regression techniques to parameterise the model. The modelling will comply with the NICE methods guide[34] including recommendations for extrapolating clinical outcomes.[35] The results of the model will be presented as incremental cost per QALY gained. Both probabilistic and deterministic sensitivity analyses will be conducted and future costs and QALYs will be discounted at the recommended rate.

12.3. Within Study Analysis

No within-study economic evaluation will be conducted, these data will be used to parameterise the economic evaluation model. As the follow-up within the trial is a minimum of 24 months, costs and effects occurring after 12 months with be discounted at the recommended rates.[34] However, in an alternative analysis (and to ensure that data are not discounted twice when used in the model) analyses will be replicated using undiscounted data.

Use of services will be combined with unit costs taken from routine data sources to produce a total NHS and cost for each participant.[31, 32, 36] Similarly, the time and travel from existing studies will be combined with information on the frequency of the use of services to produce a total time and travel cost for each participant. These costs, along with use of private health care/other out of pocket expenses, will be combined with the NHS and personal social services cost to provide an overall total cost per person. An appropriate regression model will be fitted to estimate marginal costs over the trial follow-up period whilst controlling for baseline covariates (e.g. age) clustered by site.

With respect to quality of life, participant responses to the EQ-5D-5L will be converted into utility values using the relevant UK tariff at the time of analysis. These values will be used to estimate QALYs for each trial participant using the area under the curve approach.[37] With the cost data an appropriate

regression model will be fitted to estimate marginal QALYs over the trial follow-up whilst controlling for baseline covariates (e.g. age, EQ-5D score) clustered by site.

12.4. Economic Model

For the economic model we will compare randomised treatments, with additional regimens defined following consultation with patients and clinicians. Whilst the main results of the model will be presented in terms of lifetime costs, QALYs and incremental cost per QALY, costs will be compared to those obtained from the statistical modelling. The derivation of model parameters is described in section 12.2.

Uncertainties in the model will be explored using deterministic and probabilistic sensitivity analyses. Deterministic sensitivity analysis will consider the impact of different discount rates, different time horizons and different parameter sets. Further sensitivity analyses will be presented in the form of tornado diagrams to illustrate the impact of changes in model parameters on the estimated incremental cost per QALY. In the probabilistic sensitivity analyses, suitable distributions will be assigned to each model parameter (the choice of these distributions will be guided by parameter type and standard statistical methods of their estimation but for example, gamma or log normal distributions for cost parameters, beta distribution for utility and transition probability parameters are commonly used) and Monte-Carlo simulation (which samples the parameters at random) will be performed to generate the estimates of costs and outcomes accounting for any parameter uncertainties. The results of this will be presented as cost-effectiveness acceptability curves and cost-effectiveness plane (scatter plot).

12.5. Value of Information Analysis

Using the same methods as outlined above for the development and parameterisation of the model an expected value of perfect information and the expected value of partial perfect information will be estimated and presented alongside the other results of the internal pilot. The methods adopted for the value of information analysis will follow best practice recommendations.[38]

We expect that the work presented alongside the other results of the internal pilot will make substantial use data from the literature and expert opinion as there will be relatively modest patient level data generated from the internal pilot. We also propose to replicate the value of information analysis for the final analysis, although here we expect to make full use of the trial data.

12.6. Missing Data

Patient reported outcome questionnaires will be scored using published manuals, including methods for handling missing data.

12.7. Statistical Considerations

Analyses of health economic endpoints will be conducted at LSHTM. Reference will be made to published minimally important clinical differences in patient reported outcomes where these exist. Event rates at key time points will be reported, with 95% confidence intervals.

13. TRIAL MANAGEMENT

13.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Study Chair, Chief Investigator, ICR-CTSU Methodology Lead, Co-investigators and identified collaborators, the Trial Statistician(s) and Clinical Trial Manager(s). 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. Membership will include one or more PPI representatives. Notwithstanding the legal obligations of the Sponsor, and Chief Investigator, the TMG have operational responsibility for the conduct of the trial including clinical, scientific and operational aspects.

Members of the TMG will develop and review essential trial documents. The TMG will meet at regular intervals, and at least annually to review progress of the trial. They have a responsibility to develop strategies to optimise recruitment and compliance with study procedures and to interpret study results. Details of the Committee's terms of reference, roles and responsibilities will be provided to members in a charter issued by ICR-CTSU.

13.2. Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will provide expert independent oversight of the trial on behalf of sponsor and funder. The TSC will comprise an independent Chairperson, at least two further independent members with clinical or statistical expertise (at least one member will be a statistician), a Health Economist and a lay (PPI) member.

The TSC will consider for endorsement protocol amendments proposed by the TMG that will significantly alter trial design, conduct or analysis, recommend continuation/stopping/modification of the study as part of the internal pilot; and consider the impact and relevance of any accumulating external evidence.

The TSC will meet at regular intervals, and at least annually. Details of the Committee's terms of reference, roles and responsibilities will be provided to members in a charter issued by ICR-CTSU.

13.3. Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee (IDMC) is a multidisciplinary committee responsible for safeguarding the interests of trial participants and advising the independent TSC on the continuation of the trial, taking into account the risks and benefits to the trial participants.

The IDMC will comprise a Chairperson and at least two further members with clinical or statistical expertise (at least one member will be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

The IDMC will review the emerging safety and efficacy data, assess data quality and monitor sample size assumptions. They will maintain confidentiality of all trial information that is not in the public domain advising and advise on the timing and nature of the release of any data from the trial relating to trial results or patient safety.

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 REC and the MHRA.

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

Details of the Committee's terms of reference, roles and responsibilities will be provided to members in a charter issued by ICR-CTSU.

14. RESEARCH GOVERNANCE

14.1. Sponsor Responsibilities

The sponsor of COBRA, as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, is the Institute of Cancer Research (ICR). The Sponsor's Committee for Clinical Research conducted scientific peer review as part of the approval process.

14.2. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site which is based on the UK Model Agreement for Non-Commercial Research. The local Principal Investigator is responsible for the trial team and trial conduct at the participating site.

15. TRIAL ADMINISTRATION & LOGISTICS

15.1. Site Activation

Before recruitment can commence at a site, the site agreement must have been signed by all required signatories, the required trial documentation (as specified by ICR-CTSU) must be in place and a site initiation must have taken place. Site initiation may be virtual or via on-site visit if requested by the Principal Investigator or deemed required by ICR-CTSU. ICR-CTSU will provide the final confirmation that recruitment can commence at a site.

15.2. Data Acquisition

Electronic case report forms (CRF) will be used for the collection of trial data using a purpose built CRF in the GCP compliant MEDRIO database. ICR-CTSU will provide guidance to sites to aid the completion of the CRFs. The Trial Management Group reserves the right to amend or add to the CRF as appropriate. Such changes do not constitute a protocol amendment and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

15.3. Central Data Monitoring

Once data has been entered on the CRF by the site personnel ICR-CTSU will review it for compliance with the protocol and for inconsistent or missing data in accordance with the trial's data management plan. Should any missing data or data anomalies be found, queries will be raised for resolution by the site. Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

15.4. On-Site Monitoring

If a monitoring visit is required, ICR-CTSU 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, including any electronic records, 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 protocol in accordance with the trial monitoring plan. If any problems are detected during the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

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

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

15.6. Archiving

Essential 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.

16. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

16.1. Risk Assessment and Approval

This trial has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research.

16.2. Patient and Public Involvement (PPI)

Patient and public contributors were involved in trial development and protocol design including methodology, patient information and consent forms. The participant demographic survey (DISTINCT) was developed in collaboration with PPI representatives. A PPI advisor is a co-applicant on the trial funding and PPI representatives are members of the TMG.

16.3. Ethics and Regulatory Approvals

The trial will not commence at any participating site until the required approvals are in place.

ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received favourable opinion from a research ethics committee (REC) for multi-centre trials, regulatory approval from the MHRA, HRA approval and relevant NHS Permissions. Amendments will not be implemented prior to receipt of the required approval(s).

Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

16.4. Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by ICR-CTSU and in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, the UK Policy Governance Framework for Health and Social Care, the conditions of the favourable opinion from the REC and the principles of GCP.

16.5. Informed Consent

The Principal Investigator retains overall responsibility for the conduct of research at their site; this includes obtaining informed consent from participants. The Principal Investigator must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to do so in accordance with the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki.

Patients should be asked to sign the current ethics approved COBRA 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 ethics approved COBRA patient information sheet should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

16.6. Patient Confidentiality

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

16.7. Data Protection

All investigators and trial staff must comply with the Data Protection Act 2018 at all times.

16.8. Insurance and Liability

Indemnity to meet the potential legal liability of investigators participating in this trial is provided by the usual NHS indemnity arrangements.

17. FINANCIAL MATTERS

This trial is investigator designed and led. The ICR has received funding from 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 Research Delivery Network (RDN) portfolio by virtue of its funding by the Department of Health and Social Care (DHSC). RDN resources should therefore be made available for the trial to cover UK specific research costs.

18. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared following applicable sponsor and funder policies by a writing group, consisting of members of the TMG. Participating clinicians and PPI advisors may be invited to join the writing group on the basis of intellectual and time input. All participating clinicians and PPI advisors 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. Authorship of all publications will be in accordance with ICMJE guidance.

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

All publications relating to the trial will be published open-access to comply with funder and sponsor requirements.

19. ASSOCIATED STUDIES

19.1. Health Related Quality of Life

Patient reported health related quality of life (HRQoL) is a secondary endpoint and will be analysed as described in the statistical analysis plan.

Further details are provided in Appendix A1.

19.2. Translational Sample Collection

Prospective consent will be sought for access to routinely collected bladder tumour tissue in formalin fixed paraffin blocks for future research.

Further details are provided in Appendix A2.

19.3. Equality, Diversity and Inclusion

A study within a trial (SWAT) will test an intervention to support people from socio-economically or educationally disadvantaged backgrounds to participate in COBRA.

Further details are provided in Appendix A5.

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A1. HEALTH RELATED QUALITY OF LIFE STUDY

A1.1 Background

Health-related quality of life (HRQoL) of Gem-Doce has been evaluated in a single non-randomised prospective study of patients treated with BCG (n=30) and Gem-Doce (n=30).[21, 39] There was no evidence of a difference in quality of life at baseline between the two groups but Gem-Doce patients reported significantly better overall quality of life compared to BCG at both timepoints studied – following completion of induction treatment (p=0.001) and 6 months after starting maintenance treatment (p=0.001). Gem-Doce patients had significantly better cumulative urinary symptom scores (p=0.001).

A1.2 Hypothesis

We hypothesise that Gem-Doce will be associated with an overall better quality of life and better urinary symptom scores than BCG.

A1.3 Patient Reported Outcome Measures

HRQoL will be assessed using validated gender-neutral instruments available in multiple languages:

- EORTC QLQ-F17[23] – general cancer module with a focus on functional scales
- EORTC QLQ-NMIBC24[24] – NMIBC specific module
- EQ-5D-5L[25] – generic QoL measure

The primary HRQoL outcomes of interest are overall QoL and physical functioning from the EORTC QLQ-F17 and urinary symptoms and intravesical treatment issues from the NMIBC24.

The QLQ-F17 cancer module is a shortened version of the internationally tested and validated EORTC QLQ-C30 general cancer module covering the common symptoms of cancer patients. QLQ-F17 is composed solely of items related to functioning. It includes the Physical (PF), Role (RF), Emotional (EF), Cognitive (CF) and Social Functioning (SF) scales as well as the Global Health Status/Quality of Life (QL) scale in their original wording.

The QLQ-NMIBC24 measure was developed to specifically assess QoL for patients with NMIBC. It contains six symptom scales (urinary symptoms, malaise, future worries, bloating/flatulence, sexual function, and male sexual function) and five single items (intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, and female sexual problems).

The EQ-5D measure is one of the most commonly used generic questionnaires to measure health-related QoL. The EQ-5D questionnaire consists of a questionnaire and a visual analogue scale (EQ-VAS). The EQ-VAS is a self-rated health status using a visual analogue scale. The EQ-VAS records the subject's perceptions of their own current overall health and can be used to monitor changes with time.

A1.4 Study Design

Patients are eligible for the HRQoL sub-study if they meet COBRA eligibility criteria.

Participants will be asked in the patient information sheet to consent to questionnaire completion. Those who decline to take part in the COBRA HRQoL study will remain eligible for the main trial.

A1.5 Timing of Data Collection

See section 8 for questionnaire schedule. Baseline and 3-month questionnaire booklets should be completed in clinic. Further questionnaires will be administered by ICR-CTSU.

A1.6 Missing Data

Missing data may hamper interpretation of patient-reported outcomes. Missing data may arise because participants do not complete the questionnaire at the appropriate time (unit non-response), or because patients may omit questions within the questionnaire (item non-response). Compliance with questionnaire completion will be monitored by the trial oversight committees. Analysis of missing data will be conducted in accordance with the validated instruments' scoring manuals.

A1.7 Statistical Considerations

Patient reported outcome analyses will be used to supplement results of clinician assessed treatment toxicity, therefore a formal sample size calculation has not been performed. Standard algorithms will be used to derive scores and handle missing data according to the questionnaires' scoring manuals.

Descriptive statistics will be presented for all subscales/question items. Comparative analyses will focus on the primary HRQoL outcomes of interest. A statistical analysis plan will be developed with TMG input and will specify an agreed level of statistical significance to be used for testing differences between groups. Data will be presented at each timepoint of assessment as number/percentage or medians/IQR (mean, SD) for each treatment group as appropriate. Graphical presentation will also be used, including investigating changes from pre-treatment to each time point assessed. Emphasis will be given to PRO outcomes at 2 years. Analyses to account for the longitudinal nature of the data may be used. Where published Minimal Clinical Important Differences (MCID) exist, the proportion of patients with changes from baseline exceeding the MCID threshold will be tabulated and compared using chi-square or Fisher's exact test if data are sparse.

As part of the health economics analysis HRQoL data from the EORTC QLQ-F17 and the EQ-5D-5L will be used to estimate QALYs. These data will be used to estimate the incremental cost per QALY gained (see section 12 for details).

A2. TRANSLATIONAL SAMPLE COLLECTION

A2.1 Introduction

COBRA participants will be asked to provide prospective consent for access to routinely collected bladder tumour tissue in formalin fixed paraffin blocks.

Samples will be used in future research of non-muscle invasive bladder cancer as part of separately funded translational research.

Participation in the translational sample collection is optional and participants will be asked to provide written informed consent at the time of trial entry. Participants who do not consent to provide access to routinely collected bladder tumour tissue will still be able to join the COBRA trial.

A2.2 Tissue Collection

Tissue will be collected from a participant's primary TURBT preceding trial entry and from the first recurrence following trial treatment.

FFPE tumour tissue will be requested retrospectively and will be sent to and stored at The Institute of Cancer Research. Only tissue not required for participants' diagnosis and treatment will be requested.

Any samples remaining beyond the end of trial will be transferred to an HTA licensed laboratory for storage.

A2.3 Governance and Data Linkage

Samples will be stored at The Institute of Cancer Research in accordance with its 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.

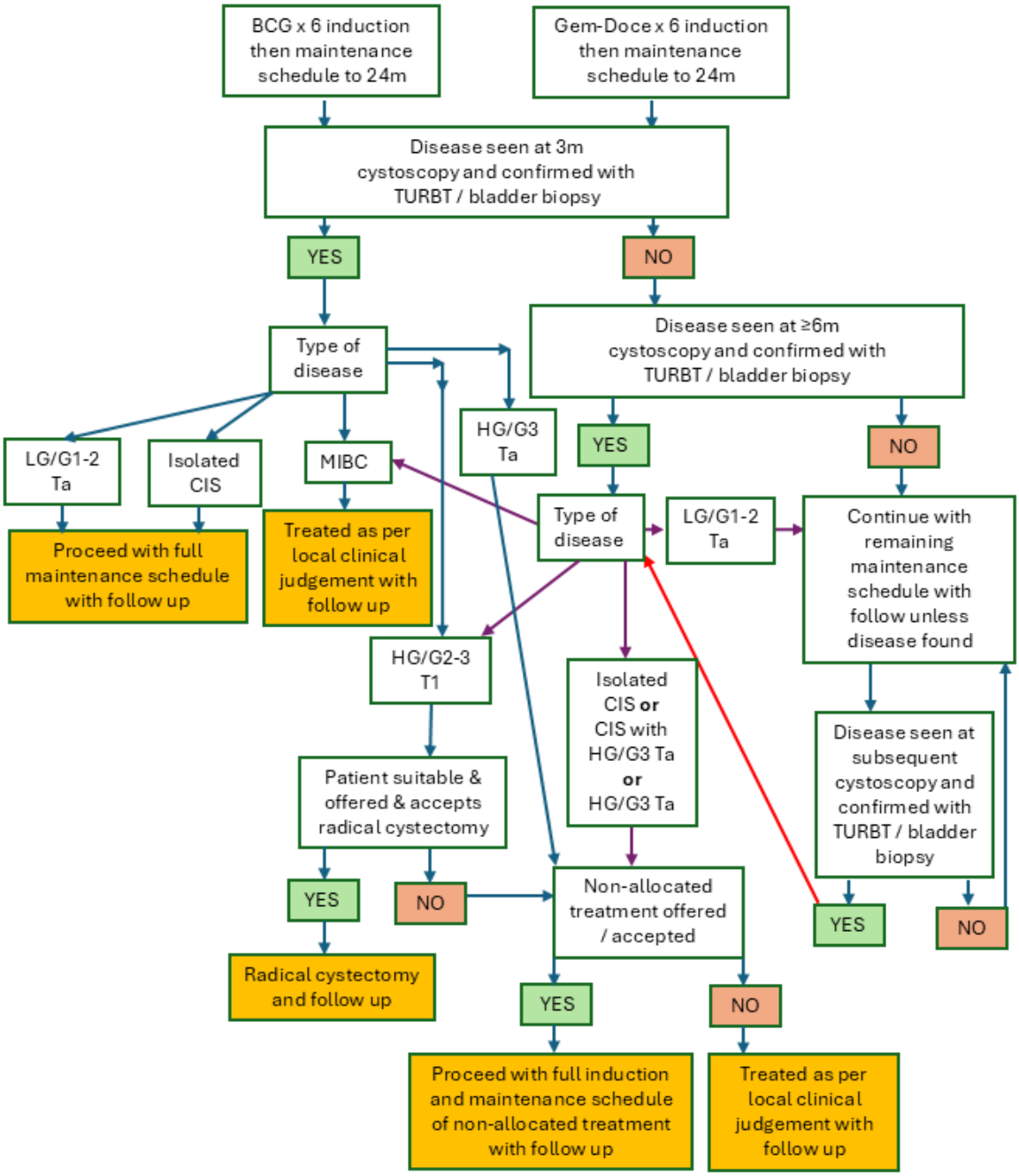
A2.4 Sample Custodianship and Access Arrangements

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

A3. WHO PERFORMANCE STATUS

Grade	Performance Status
0	Able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

A4. FLOWCHART OF REQUIRED PROCEDURES AT DISEASE PROGRESSION/RECURRENCE



A5. EQUALITY, DIVERSITY AND INCLUSION (EDI) STUDY WITHIN A TRIAL

A5.1 Background

A Study Within a Trial (SWAT) will test a co-developed intervention to support participation of people from socio-economically or educationally disadvantaged backgrounds.

The intervention will be implemented for evaluation at selected participating sites via substantial amendment.

A6. GLOSSARY

AE	Adverse Event
BCG	Bacillus Calmette-Guerin
CI	Chief Investigator
CIS	Carcinoma In Situ
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DHSC	Department of Health and Social Care
EDI	Equality, Diversity and Inclusion
EORTC	European Organisation for Research and Treatment of Cancer
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
Gem-Doce	Gemcitabine-Docetaxel
HE	Health Economics
hgRFS	high grade Recurrence-Free Survival
HR	Hazard Ratio
HRA	Health Research Authority
HR-NMIBC	High risk non-muscle invasive bladder cancer
ICMJE	International Committee of Medical Journal Editors
ICR	The Institute of Cancer Research
ICR-CTSU	The Clinical Trials Statistics Unit at The Institute of Cancer Research
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
LSHTM	The London School of Hygiene & Tropical Medicine
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NIHR-HTA	National Institute for Health and Care Research Health Technology Assessment
NICE	National Institute for Health and Care Excellence
NMIBC	Non-muscle invasive bladder cancer
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and public involvement
PSA	Prostate-Specific Antigen
QALY	Quality adjusted life year
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised controlled trial
RDN	Research Delivery Network
REC	Research Ethics Committee
RFS	Recurrence-free survival
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within A Trial
TMG	Trial Management Group
TSC	Trial Steering Committee
TURBT	Transurethral resection of bladder tumour
VAS	Visual analogue scales
WHO	World Health Organisation

A7. HISTORY OF PROTOCOL AMENDMENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES
Version 4.0 20/01/2026	• **Section 9.1.1:** Clarification that any BCG licensed for intravesical use in the UK can be administered by the participating site in accordance with their local policy. • **Section 9.1.1:** Amended BCG dose from 50mg to one dose per instillation. • **Section 9.1.3:** Additional guidance to check the final concentration of the local stock formulation is within stability range limits. • **Section 9.1.4:** Additional guidance to check the final concentration of the local stock formulation is within stability range limits. • **Section 9.6.2:** Amended table to clarify permissible dose modifications in relation to one dose of BCG and removal of 1/100 dose as a permitted reduction.
Version 3.0 25/11/2025	• **TRIAL COORDINATION:** Updates to administrative details. • **Section 9.1.4:** Amended sodium chloride volume to meet docetaxel stability requirements. • **Section 10.1.1:** Updated to adhere to MHRA clinical conditions of approval – expected events and RSI for gemcitabine and docetaxel amended accordingly. • **Section 11.5**: Updated to include the complete pilot progression criteria. • **Section 19.3**: Updated to include reference to the EDI SWAT. • **Appendix 5:** Added appendix for the EDI SWAT which will be implemented via a future substantial amendment. • **Appendix 6 and 7:** New appendix number assigned.
Version 2.0 25/09/2025 (changes from v1.0 03/07/2025)	• Updates to trial identifiers • Updates to trial coordination contact details • Updates to trial schema to reflect main protocol changes • **Section 5.5:** Updated to state that male participants must use condoms for the duration of the trial and 6 months following the last dose of trial treatment. • **Section 8:** Updated to include assessment of safety bloods, physical examination and assessment of vital signs at specified time points during the trial. • **Section 8.3:** Updated to include an additional pregnancy test at week 4 of the induction treatment schedule. • **Section 9.8:** Updated to state that any investigational medicinal product (for any indication) and any live vaccine are not permissible during study participation. • **Section 9.12:** Updated to confirm there are no plans to provide trial treatment beyond the end of trial and patients will revert to standard of care. • **Section 10.1:** Updated to state that SAEs will be recorded from the date of randomisation. • **Section 13:** Updated to outline the roles and responsibilities of the various trial oversight committees.

	• **Section A2.2:** Updated to confirm that any samples remaining beyond the end of trial will be transferred to an HTA licensed laboratory for storage.