TRAIN

A Phase III randomised control clinical trial of radiotherapy with radiosensitisation versus intravesical Bacillus Calmette-Guerin therapy for high-risk non-muscle invasive bladder cancer - TRAIN

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FUNDER

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Protocol Information

This protocol describes the TRAIN trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will be conducted in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
BAUS	British Association of Urological Surgeons
BCON	Bladder Carbogen and Nicotinamide
BCG	Bacillus Calmette-Guérin
cfDNA	Cell free DNA
CI	Chief Investigator
CINV	Chemotherapy-Induced nausea and vomiting
CIS	Clinically Isolated Syndrome
CON	Carbogen and Nicotinamide
CEAC	Cost Effectiveness Acceptability Curve
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTCs	Circulating Tumour Cells
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Reports
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Safety Report Form
EORTC	The European Organisation for Research and Treatment of Cancer
EUA	Emergency Use Authorizations
FBC	Full Blood Count
GA	General Anaesthetic
GCP	Good Clinical Practice
G3	Grade three
HR-NMIBC	High-Risk Non-Muscle Invasive Bladder Cancer
HSG	Hysterosalpingogram
IB	Investigator Brochure
ID	Identification
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IPSS	International Prostate Symptom Score
LFT	Liver Function Test
MDT	Multi-Disciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-Free Survival
MHRA	Medicines and Healthcare products Regulatory Agency
MO	Medical Officer
MIBC	Muscle Invasive Bladder Cancer
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NHS	National Health Service
NMIBC	Non- Muscle Invasive Bladder Cancer
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator

PID	Patient Identifiable Data
PIS	Participant Information Sheet
PRO	Patient reported outcomes
REC	Research Ethics Committee
RTOG	Radiation Therapy Group
RTTQA	National Radiotherapy Trials Quality Assurance Group
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SCTU	Southampton Clinical Trials Unit
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Tri-modality treatment
TSC	Trial Steering Committee
TURBT	Trans Urethral Resection of Bladder Tumour
UAR	Upper Airway Resistance
U&E	Urea and Electrolytes
WHO	World Health Organisation
WOCBP	Woman Of Childbearing Potential

KEYWORDS
non-muscle invasive bladder cancer, Bacillus Calmette-Guerin therapy, radiotherapy with radiosensitisation

TRIAL SYNOPSIS

Short title:	**TRAIN**
Full title:	A Phase III randomised control clinical trial of radiotherapy with radiosensitisation versus intravesical Bacillus Calmette-Guerin (BCG) therapy for high-risk non-muscle invasive bladder cancer (HR-NMIBC).

Phase:	Phase 3
Population:	Patients with histologically confirmed grade 3 T1N0M0 transitional cell carcinoma or carcinoma-in-situ of the bladder (or both). Following review within a designated bladder cancer multidisciplinary team, patients will have been recommended for BCG treatment. They will be BCG therapy-naive and will have undergone 'maximal TURBT'. They will be suitable for treatment in either arm of the trial. **Inclusion Criteria** • Diagnosed with histologically confirmed grade 3 T1 N0 M0 transitional cell carcinoma, OR carcinoma in situ of the bladder (and N0 M0), OR both, with detrusor muscle present in the biopsy specimen if T1 disease (or a repeat resection that does contain muscle that is clear) • Suitable for BCG treatment • Suitable for radiotherapy and radiosensitisation according to the schedule of administration outlined in the Radiotherapy Planning Guidance document. • Life expectancy over 12 months • ECOG performance status 0 – 2 • Age >=16 years • Provided written informed consent **Exclusion Criteria** • MDT selected patients with HR-NMIBC who are deemed best suited for primary cystectomy (patients that have had this treatment recommendation but then decline cystectomy remain eligible for TRAIN) • Previous radiotherapy to the pelvis • Previous intravesical therapy • Poor bladder function (IPSS >16) • A recent or current other cancer. Current non-melanoma skin cancer, cervical carcinoma in situ or localized prostate cancer not requiring current treatment are permissible, as is a history of a separate other malignancy having completed all active treatment ≥2 years previously and without evidence of relapse • Pre-existing medical conditions that preclude treatment options in either trial arm • Pregnant or breast-feeding • Not able to use appropriate adequate effective contraception during and for up to 6 months after the study (see section 7.4.3) • Hypersensitivity to the IMP's or any of their excipients • Any other contraindications to treatment with the study IMPs as per their approved SmPCs

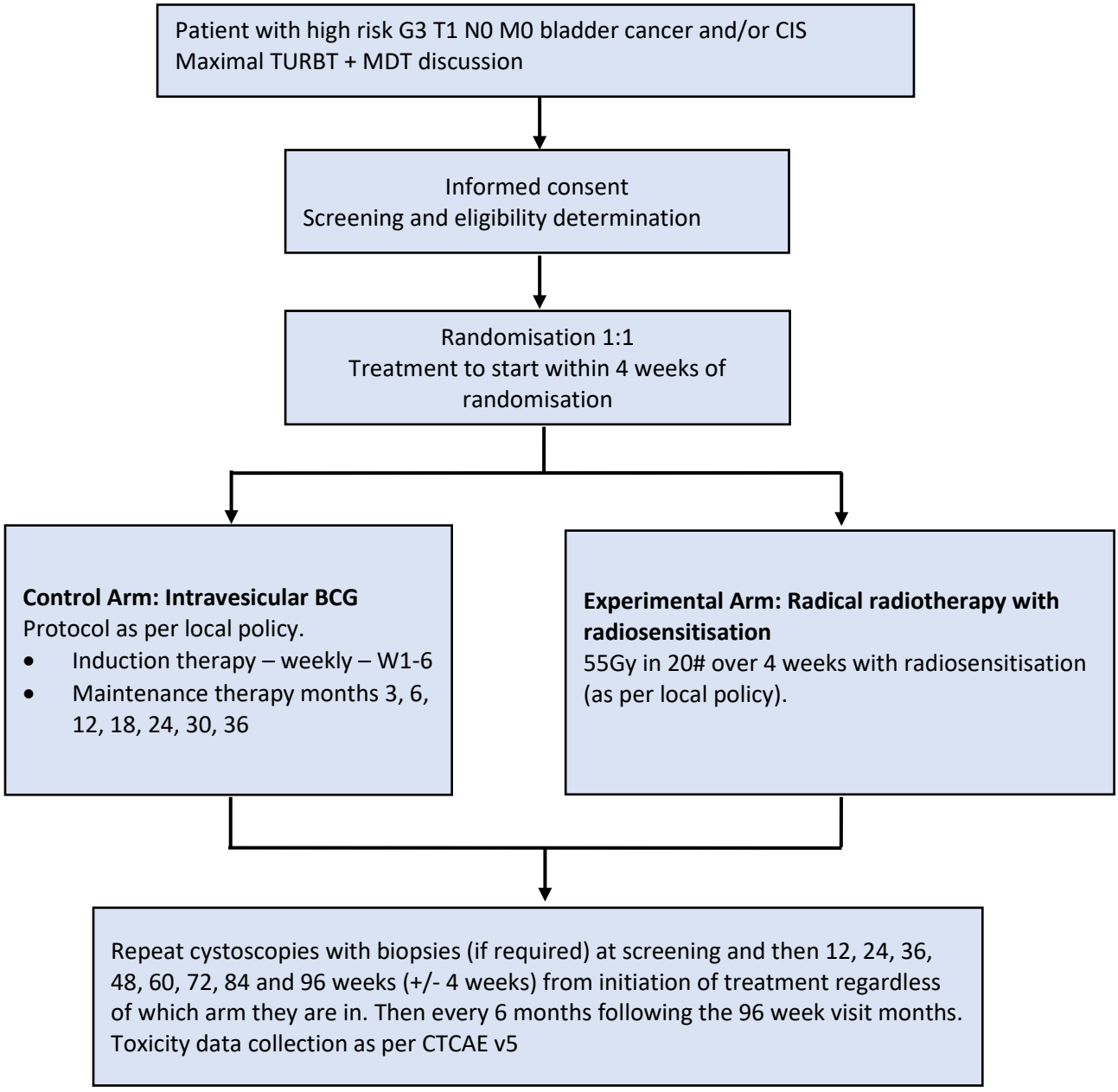
Primary Objective:	To compare event-free survival between BCG and radiotherapy with radiosensitisation.
Secondary Objective:	• To compare each component of the primary outcome between BCG and radiotherapy with radiosensitisation. • To determine the difference between BCG and radiotherapy with radiosensitisation for patient-reported symptoms. • To determine the difference in cancer specific survival between groups. • To establish tolerability and safety of radiotherapy with radiosensitisation. • To determine the difference in treatment fidelity between the groups. • To determine the cost-effectiveness of radiotherapy with radiosensitisation compared to BCG.
Rationale:	Radiotherapy with radiosensitisation is an established treatment for patients with MIBC, providing an alternative option to radical cystectomy. The evidence for chemo-radiotherapy in high-risk NMIBC is not established, but a meta-analysis of published data confirms efficacy in over 50% of patients with radiotherapy alone. At present, these patients receive intravesical BCG, which carries a significant risk of relapse or progression. There are also intermittent problems with supply of BCG.
Trial Design:	This is an unblinded, superiority, parallel group, randomised phase III trial with internal pilot, interim futility analysis and cost-effectiveness assessment. The trial will randomly allocate patients equally between the standard of care (BCG) and radiotherapy with a radiosensitiser.
Sample size:	The sample size was calculated using the *rpact* package in R for group sequential designs, using alpha = 0.025 (one-sided), power = 0.9 (with O'Brien-Fleming boundaries to control type II error), hazard ratio = 0.5, and a piecewise exponential survival distribution with event rate in the control arm of 10, 20, 25 and 30% at 3, 6, 12 and 24 months. With accrual time of 36 months and minimum follow-up time of 24 months, the required sample size is 312 patients. Accounting for 5% drop out, the final sample size is 328. An interim analysis for futility will take place when 50% of the information in the outcome has been collected.
Experimental Arm:	Radiotherapy - 55Gy in 20 fractions treating once daily Monday to Friday over 4 weeks. Radiosensitiser as one option from the following: • Gemcitabine 75: 100mg/m^2 via intravenous infusion administered once a week during a four-week radiotherapy course. Cycle 1 will be given on the first radiotherapy day, to a planned total of 4 cycles. Administered 2 to 4 hours prior to radiotherapy • 5-FU and Mitomycin C: Fluorouracil 500 mg/m^2 on days 1 to 5 and 16 to 20 via continuous infusion. Mitomycin C 12 mg/m^2 on day 1 via intravenous infusion • Carbogen and nicotinamide (CON): Carbogen (2% CO_2 and 98% O_2) will be delivered through a closed breathing system with an expansion bag and one-way valve. Either an airtight face mask or mouthpiece with nasal clip will be used to deliver the carbogen. Carbogen breathing will be started 5 minutes before radiotherapy and continued during each fraction of

	radiotherapy delivery. Carbogen breathing will be given daily with each fraction of radiotherapy. Oral nicotinamide of 40-60mg/kg will be taken 1.5 to 2 hours before radiotherapy.
Control Arm:	Standard of care BCG at each centre (BCG protocol of 6 weekly intravesical instillations, followed by 3 weekly instillations at 3, 6, 12, 18, 24, 30, 36 months) In the event of BCG shortage, a nationally recognised alternative to a BCG protocol may be given (e.g., as outlined by BAUS; if this was indicating cystectomy then the patient would be considered ineligible)
Dosage Regimen / Duration of Treatment:	See above

URL for Database:	https://www.imedidata.com
URL for randomisation:	https://prod.tenalea.net/ciru/DM/DELogin.aspx

Primary Trial Endpoints:	Event-free survival between treatment arms defined as time from randomisation to any of: CIS or high-risk G3 non-muscle invasive papillary tumour recurrence, continued presence of HR NMIBC even after treatment completion, progression to muscle-invasive disease, distant metastatic bladder cancer, cystectomy (for any reason) or death from any cause. Patients will be censored at the point of last follow-up where an event has not occurred. Cystoscopies will be every 3-4 months as per standard of care and in accordance with NICE guidelines to capture progression and recurrence data.
Secondary Trial Endpoints:	• Recurrence-free survival • Progression-free survival • Metastasis-free survival • Cancer specific survival • Cystectomy-free survival • Overall survival • Treatment fidelity • Adverse events (CTCAEv5.0) • Cost-effectiveness: HE(ModRUM) • Late radiation morbidity of the bladder and intestines (RTOG – see Appendix A) • Patient-reported outcomes: EQ-5D, IPSS, QLQ-C30 and QLQ-NMIBC24
TRAIN-Gen Translation Study:	The TRAIN patients' biospecimens will contribute to the TRAIN-gen programme of translational research, funded by an NIHR i4i Product Development Award (NIHR505393). The objectives of TRAIN-gen are: • To evaluate whether a proportion of surveillance flexible cystoscopies can be omitted during the follow-up of HR-NMIBC patients by the use of the GALEAS™ Bladder urine test, thereby improving patient quality-of-life and reducing healthcare costs. • To identify specific subgroups of patients who do/do not respond to BCG and/or radiotherapy, thereby permitting personalised therapy recommendations.
Total Number of Sites:	Approximately 12-20 UK sites

TRIAL SCHEMA



SCHEDULE OF OBSERVATIONS AND PROCEDURES

	Screening (within 28 days prior to randomisation)	Baseline (pre-rand but within 4 weeks of screening)	Within 4 weeks post randomisation	From initiation of treatment										
				2 weeks + / - 1 week	4 weeks + / - 1 week	12 weeks +/- 4 weeks	24 weeks +/- 4 weeks	36 weeks +/- 4 weeks	48 weeks +/- 4 weeks	60 weeks +/- 4 weeks	72 weeks +/- 4 weeks	84 weeks +/- 4 weeks	96 weeks +/- 4 weeks	Every 6 months (+/- 4 weeks) up to end of trial[10]
Informed Consent	x													
Medical history	x													
Concomitant medication record	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cystoscopy (+/- TURBT and biopsy as required)	x					x	x	x	x	x	x	x	x	x[8]
CT urogram	x[1]												x	
FBC	x[2]			x	x				x				x	
U&E	x[3]			x	x				x				x	
LFTs & bone profile	x[3]			x	x				x				x	
Urine cytology	x[3]					x	x	x	x	x	x	x	x	x
Pregnancy test[14]	x													
ECOG performance status	x			x	x	x	x	x	x	x	x	x	x	x
Physical exam and vital signs	x			x	x	x	x	x	x	x	x	x	x	x
Eligibility check	x													
Randomisation		x												
RTOG late morbidity							x	x	x	x	x	x	x	x
CTCAE V5		x[12]	x	x	x	x	x	x	x	x	x	x	x	x
EORTC QLQ-C30		x[11]				x	x	x	x	x	x	x	x	
EORTC QLQ-NMIBC24		x[11]				x	x	x	x	x	x	x	x	
EQ-5D		x[11]				x	x	x	x	x	x	x	x	
IPSS		x[11]				x	x	x	x	x	x	x	x	x
HE (ModRUM)							x							
Treatment – BCG [4]			x[5]			x	x		x		x		x	x
Treatment – radiotherapy [6]			x[5]											
Treatment – radiosensitiser [7]			x[5]											
Diagnostic tumour block		x												
Translational blood sample[9]		x				x	x							
Translational urine sample[15]		x				x	x							
Survival status														x[13]

[1] Diagnostic CT urogram within 3 months of randomisation. Repeat every 2 years.
[2] Haematology including Full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelets counts
[3] Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium)
[4] Standard of care BCG at each centre (BCG protocol of 6 weekly intravesical instillations, followed by 3 weekly instillations at approximately 3, 6, 12, 18, and 24 months, then 6-monthly up to 3 years).
[5] Refers to initiation of treatment.

[6] Radiotherapy (experimental intervention) - 55 Gy in 20 fractions treating once daily Monday to Friday over 4 weeks

[7] Radiosensitiser options listed in section 6.2 'Radiotherapy arm'

[8] The cystoscopy can be local anaesthetic flexible cystoscopy, as per clinical preference. The cystoscopy conducted at screenng may be done within 6 weeks prior to randomisation. Cystoscopies should be conducted at screening and then 12 weeks (+/- 4 weeks) from initiation of treatment regardless of which arm they are in, then repeated every 6 months following the 96 week visit.

[9] Four translational blood samples to be taken in total. At baseline, 12 weeks and 24 weeks from the start of treatment (+/- 4 weeks) and either at the end of treatment or patient progression (whichever event occurs first and again within +/- 4 weeks from event). Samples should be taken and sent the same day (except Friday, Saturday and Sunday) to the Manchester Cancer Research Centre HTA licensed Tissue Bank.

[10] See section 5.6 for details on follow-up following recurrence or progression.

[11] These measures will ideally be taken pre-randomisation, but where required, these can be collected following randomisation prior to treatment initiation.

[12] All protocol reportable AEs and SAEs should be reported from consent up to the end of the follow-up period (not including the remote survival status follow-up). Between consent and randomisation only AEs and SAEs that are trial related should be reported

[13] Survival status should be reviewed and recorded every 6 months (+/- 4 weeks) until the end of the study. This includes any recurrence or progression event. See section 5.6. When follow-up in the trial is anticipated to be close to completion, a final round of data collection will be carried out to ensure that survival information is up-to-date.

[14] Pregnancy test to be completed at screening and then as per standard of care for WOCBP.

[15] Translational urine samples should be taken and sent the same day (except Friday, Saturday and Sunday) to Manchester Cancer Research Centre HTA licensed Tissue Bank.

1 INTRODUCTION

1.1 BACKGROUND

In the UK 20,000 people develop urothelial type bladder cancer every year of which 75-80% have non-muscle invasive disease [1]. This may be underestimated as the National Cancer Registration and Analysis Service (and CRUK) does not include all non-muscle invasive bladder cancer (NMIBC) cases. Bladder cancer causes 5,500 deaths each year [2]. NMIBC includes those staged as < T2 N0 M0, meaning the tumour has not spread as far as the muscle layer of the bladder wall or beyond the bladder. Bladder cancer commonly affects older people (70% are over 65 years) [3]. NMIBC is one of the most expensive cancers to treat on a per-patient basis due to the need for long-term surveillance that includes cystoscopies [4].

Standard of care (SoC) for high-risk (HR) NMIBC (T1 grade 3 [T1G3]/CIS) is either through transurethral resection of bladder tumour (TURBT) followed by a course of intravesical Bacillus Calmette-Guérin (BCG), or radical cystectomy. Compared to BCG, data suggests that disease-specific survival is better with cystectomy, but many patients wish to preserve their bladder and avoid a stoma, and at least 25% are not fit for major surgery.

BCG is given once weekly for six weeks (induction course) followed by maintenance treatments which last for up to 3 years. However, 50% of patients will experience cancer recurrence after BCG, and side effects result in 1 in 4 stopping treatment [5, 6]. These include bacterial (26%) or BCG cystitis (47%), frequency of passing urine (>1/hr) (31%), blood in the urine (34%), fever (15%), malaise (23%), arthralgia (5%), and lung infection (0.2%) [4, 5].

HR-NMIBC (T1G3) can recur despite TURBT and BCG, with a substantial rate of progression to muscle-invasive bladder cancer (44%; MIBC) [7]. Once it progresses to MIBC, bladder cancer becomes a substantial risk to life. In patients who progress to MIBC the outcome is worse than in those presenting with primary MIBC. Cancer-specific survival at 3 years is 67% vs 37% in the primary versus progressive setting [7].

Radical cystectomy is reserved for BCG failure and occasionally as a primary treatment. In patients undergoing radical surgery outcomes are good but no trial has been able to randomise patients successfully. The BRAVO study attempted to do so and was unable to randomise enough patients, but in those who did proceed to cystectomy (n = 20) all were free of disease at 12 months [8]. In general terms, radical cystectomy efficacy must be balanced with the significant morbidity of major surgery with bladder removal, and the potential change in the quality of life for patients with urinary diversion. BRAVO shows that patients often prefer bladder preservation strategies.

To compound the limitations of current treatment options, BCG supply has failed globally several times over the last 7 years [9]. A recent study evaluated the clinical and economic impact of BCG shortage on NMIBC patients treated during the period of restricted supply and concluded there was an increased rate of bladder cancer recurrence, and the total cost of care for HR-NMIBC was increased [10].

A European study, involving 3401 individual patient datasets across multiple institutions, found 50% of HR-NMIBC progressed to MIBC. Many patients have side effects from intravesical therapy, with 25% ceasing treatment [6]. BCG therapy causes side effects in up to 75% [5, 6]: both local and systemic. Due to industrial production problems, BCG has had several episodes of low supply over the last 7 years [10]. This has led to national organisations like the British Association of Urological Surgeons (BAUS) implementing different regimens to overcome supply problems. This included reducing the length of BCG treatment, using mitomycin or proceeding directly to cystectomy. However, reducing the length of BCG treatment results in increased recurrence [10-12].

The standard practice for recurrence on BCG therapy (BCG-refractory disease) is to proceed to early radical cystectomy [13-14]. However, cystectomy is associated with mortality (3%), high rates of postoperative

complications of nearly 50% at 30 days and often requires a permanent stoma affecting the patient's quality of life [15, 16].

There is, therefore, a pressing need to provide alternative treatment options. These should ideally improve the prevention of cancer recurrence and progression and reduce the need for the life-altering option of cystectomy. We should also remove our current reliance on a recurrently unpredictable supply of a drug and be cost-effective. The TRAIN trial will attempt to do this through a fundamental change in treatment approach.

Bladder preservation with radiotherapy and radiosensitisers is an equivalent and alternative treatment to radical cystectomy for MIBC [13, 17]. A meta-analysis comparing outcomes for radical cystectomy and bladder preservation showed no difference in overall survival (OS), disease-specific survival or progression-free survival with slightly higher early complications in the surgical group. 5-year OS was estimated at 56.2% with radical cystectomy and 55.0% with bladder preservation [17].

The strongest evidence for using radiosensitisation in MIBC is from the phase III BC2001 [18] and BCON [19] trials. These trials resulted in radiosensitisation becoming the standard of care worldwide. Although the BC2001 [18] trial only included T2 disease or greater, 9.2% in the BCON trial [19] had high-risk T1 disease. Another schedule is weekly gemcitabine combined with hypofractionated radiotherapy (GemX) [20].

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

Currently, TURBT followed by radiotherapy with a radiosensitiser, also called tri-modality treatment (TMT), is not a standard treatment for NMIBC. A previous UK trial, randomised 210 patients with NMIBC between BCG and radiotherapy alone, showing no significant difference in response between the two arms for the primary endpoint of progression-free interval at 5 years HR 1.07 (95% CI:0.65-1.74 p=0.785) [21]. Importantly, this trial completed recruitment two decades ago, using now outdated techniques and no radiosensitiser.

A systematic review [22] evaluated 13 studies including 746 patients with HR-NMIBC treated with primary TMT. The 5-year rates of recurrence-free survival, cancer-specific survival and overall survival were 54% (95% CI = 38-70%), 86% (95% CI = 80-92%), and 72% (95% CI = 64-79%). Notably, 13% of patients proceeded to salvage radical cystectomy and 9% developed metastatic disease. These results are promising and suggest that TMT is an effective treatment for NMIBC. The systematic review highlighted the need for a prospective clinical trial to clearly define the risks and benefits of this treatment approach [22].

A recent phase II trial, RTOG-0926 [32], investigated the benefit of TMT in recurrent NMIBC following intravesicular treatment. Patients were recruited between 2009-2017 and received chemoradiotherapy (61.2 Gy in 34 fractions) with radio-sensitizing cisplatin or mitomycin/5-FU chemotherapy. Initial data is favourable with three-year freedom from cystectomy rate of 88% and overall survival at 5 years of 53% (95% CI: 35%, 72%). The rate of distant metastatic disease at 5 years was 20% (95% CI: 8%, 37%) [23].

Biomarkers could potentially identify relatively radio-responsive T1 disease as opposed to those that would be better treated with either BCG or cystectomy. From the BCON trial, we showed that both necrosis and HIF-1α identify patients who respond to hypoxia modification [24]. Among patients with necrosis, 5-year OS was 34% after radiotherapy alone versus 56% after radiotherapy and CON (p = 0.004) [25]. MRE11, which is involved in DNA-damage signalling, at both the protein and germline levels is associated with better cancer-specific survival [26-28]. Samples will be collected from this trial for biomarker discovery and validation.

We will test if modern hypofractionated radiotherapy with radiosensitisation can lead to superior rates of long-term control and bladder preservation when compared to intravesicular BCG in high-risk and very high-risk NMIBC. If successful, this study will change practice for patients across the UK and worldwide.

Ongoing clinical trials

The current focus of phase III trials in NMIBC is to augment the immune reaction of BCG using systemic immune-modulating agents, while BCG alone stands as the standard of care (SoC). If the SoC were to change, we will reassess and consider methods for changing the control arm to reflect this. Other experimental interventions (e.g., TAR200, intravesical chemotherapy) are further back in development and unlikely to replace the BCG control arm as SoC during the lifetime of this trial. These experimental options are expensive, and intensive for both patients and healthcare services and there is limited data on long-term toxicity. In contrast, the long-term toxicity of radiotherapy with radiosensitisation is well documented [29].

1.2.1 Risks

I. Radiotherapy

Radiotherapy will be delivered by the direct healthcare team. Clinician-reported toxicity will be collected using the 'Common Terminology Criteria for Adverse Events' Version 5.0 Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov). Radiotherapy is associated with fatigue, dysuria and frequency, bowel urgency and frequency. The addition of chemotherapy can cause myelosuppression. Peripheral blood counts are monitored, and indices may fall. Late effects include recurrent urinary tract symptoms, chronic bowel frequency, and in premenopausal women the effects of ovarian ablation.

II. Chemotherapy

Although chemotherapy dose is much lower than as a primary systemic treatment, gemcitabine can still rarely cause side effects. These include thrombocytopenia (common), leukopenia, neutropenia, anaemia, nausea, and non-haematological events such as myalgia/flu-like symptoms (~17% mod/severe), asthenia (~21%mod/severe), LFT derangements, CINV; rarely, microangiopathic haemolytic anaemia/ haemolytic uraemic syndrome have been reported in literature as being an idiosyncratic drug reaction.

III. Intravesicular BCG:

The most frequent local side effects of BCG are the BCG-induced cystitis (35%) and bacterial infection (23.3%), frequency of urination of more than once per hour in 23.6%, and macroscopic haematuria in 22.6% of patients. The most frequent systemic side effects were general malaise in 15.5% and fever in 8.1% [30].

IV. Repeat Cystoscopies

Clinical assessment will be by cystoscopy with EUA and biopsy of any visualised abnormalities. Follow-up cystoscopies at 3 and 6 months will be carried out under general or spinal anaesthetic (GA) and require 2 random biopsies of normal mucosa. GA and biopsies/resections have associated risks. Any recurrences will require a re-discussion at the MDT to consider salvage therapy.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 PRIMARY TRIAL OBJECTIVE AND ENDPOINT

Primary objective: to compare event-free survival between BCG and radiotherapy with radiosensitisation.

Event-free survival between treatment arms is defined as time from randomisation to any of: CIS or high-risk G3 non-muscle invasive papillary tumour recurrence, progression to muscle-invasive disease, distant metastatic bladder cancer, cystectomy (for any reason) or death from any cause. Patients will be censored at the point of last follow up where an event has not occurred. Cystoscopies will be every 3 months as per standard of care and in accordance with NICE guidelines to capture progression and recurrence data.

2.2 TABLE OF ENDPOINT/OUTCOMES

	Objective	Outcome Measures	Summary method(s)
Primary	To compare event-free survival between BCG and radiotherapy with radiosensitisation.	Event-free survival is defined as recurrence of CIS or high-risk non-muscle invasive papillary tumour, continued presence of HR NMIBC even after treatment completion, progression to muscle-invasive disease, distant metastatic bladder cancer, cystectomy (for any reason) or death from any cause.	• Primary: Event-free survival will be analysed using Cox proportional hazards model to calculate a hazard ratio, 95% confidence interval and p-value for group allocation, adjusted for stratification factors. • Summary of Kaplan-Meier estimates of event rates by group at 12 and 24 months. • Kaplan-Meier plot of EFS by group.
Secondary	To determine the difference between BCG and radiotherapy in terms of patient-reported symptoms	Patient reported outcomes – RTOG (late bladder and intestinal toxicity), EQ-5D, IPSS, QLQ-C30, QLQ-NMIBC24	Questionnaire data will be summarised by group and timepoint.
	To evaluate each component of the primary outcome comparing between BCG and radiotherapy with radiosensitisation.	• Recurrence-free survival (RFS) defined as time from randomisation to recurrence of non-muscle invasive papillary tumour. Patients are censored at the last follow-up if event free. • Progression-free survival (PFS) defined as time from randomisation to progression to muscle-invasive disease. Patients are censored at the last follow-up if event free. • Metastasis-free survival (MFS) defined as time from randomisation to progression to distant metastatic bladder cancer.	• Each event outcome will be analysed using Cox proportional hazards model to calculate a hazard ratio, 95% confidence interval and p-value for group allocation, adjusted for stratification factors. • Summary of Kaplan-Meier estimates of event rates by group at 12 and 24 months. • Kaplan-Meier plot by group.

		Patients are censored at the last follow-up if event free. • Cystectomy-free survival (CFS) defined as time from randomisation to cystectomy. Patients are censored at the last follow-up if event free • Overall survival (OS) defined as time from randomisation to death due to any cause. Patients are censored at the last follow-up if event free	
	To establish the tolerability and safety of radiotherapy	MedDRA coded adverse events graded using CTCAE v5.0.	Summaries of adverse event data will be presented by group (including serious adverse events)
	To determine the difference in cancer specific survival between groups.	Cancer specific survival defined as time from randomisation to death from cancer. Patients who die of a cause other than the cancer under study or who are lost to follow-up are censored at death or the last date on which they were known to be alive.	Summary of event rates by group at 12 and 24 months.
	To determine the difference in treatment fidelity between the groups	Treatment fidelity defined as how well each group implemented treatment as intended	Summary statistics will be presented for treatment delays, missed treatment, those not starting treatment, and those who completed treatment, by group
	To determine the cost-effectiveness of radiotherapy with radiosensitisation compared to BCG	• Within trial analysis. Total costs and QALYs for radiotherapy with radiosensitisation compared to BCG during the trial period. • Economic modelling. Total costs and QALYs for radiotherapy with radiosensitisation compared to BCG extrapolated beyond the trial period.	• Health care resources HE (ModRUM) during the follow-up period will be calculated and combined with cost data to estimate total costs. EQ-5D 5L data will be converted to EQ-5D 3L and the total QALYs will be calculated using 'area under the curve' method. • An economic model will be constructed to describe the transition between disease recurrence, progression and death over a time horizon

			of 20 years. Results will be presented as an incremental cost effectiveness ratio, and with a cost-effectiveness scatterplot and CEAC curve. Uncertainty will be explored with deterministic and probabilistic sensitivity analysis.

3 OVERALL TRIAL DESIGN

TRAIN aims to assess if radiotherapy with radiosensitisation can improve outcomes for high-risk and very high-risk (G3/cis) non-muscle invasive bladder cancer compared to current standard treatment.

This is a phase 3 multicentre, open label, parallel group, randomised controlled trial with internal pilot, futility interim analysis, and health economic evaluation, comparing usual care (BCG) with a radiotherapy and radiosensitiser. This is the gold-standard design for comparing the clinical and cost effectiveness of the proposed new treatment. Due to the nature of the interventions being assessed, blinding is unfeasible and unethical (as this would require sham catheterisation and radiotherapy, placing unjustifiable burden on NHS resources and participants).

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 CONSENT

The Principal Investigator (PI) retains overall responsibility for the conduct of the research at their site, including the receipt of informed consent from participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, GCP trained, and competent to do so.

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a Participant Information Sheet (PIS) offered, and time allowed for consideration. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purpose of the trial.

The right of the participant to refuse to participate without giving reasons must be respected.

After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if they feel it is in the participant's best interest, but the reasons for doing so should be recorded.

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment or their legal rights. Participants must be provided with a contact point where they may obtain further information about the trial.

Upon completion of the informed consent form, a copy will be given to the patient, a copy stored in the patient's medical notes, the original filed in the site trial file and a copy of the consent form be sent to the SCTU using the University of Southampton's SafeSend service – email address: monitorSCTU@soton.ac.uk or monitorSCTU@securemail.soton.ac.uk – to allow for central monitoring.

4.2 INCLUSION CRITERIA

Patients with histologically confirmed grade 3 T1N0M0 transitional cell carcinoma or carcinoma-in-situ of the bladder (or both). Following review within a designated bladder cancer multidisciplinary team, patients will have been recommended for BCG treatment. They will be BCG therapy-naive and will have undergone 'maximal TURBT'. They will be suitable for treatment in either arm of the trial.

1. Diagnosed with histologically confirmed grade 3 T1 N0 M0 transitional cell carcinoma, OR carcinoma in situ of the bladder (and N0 M0), OR both, with detrusor muscle present in the biopsy specimen if T1 disease (or a repeat resection that does contain muscle that is clear)
2. Suitable for BCG treatment
3. Suitable for radiotherapy and radiosensitisation according to the schedule of administration outlined in the Radiotherapy Planning Guidance document.
4. Life expectancy over 12 months
5. ECOG performance status 0 – 2
6. Age >=16 years
7. Provided written informed consent

4.3 EXCLUSION CRITERIA

1. MDT selected patients with HR-NMIBC who are deemed best suited for primary cystectomy (patients that have had this treatment recommendation but then decline cystectomy remain eligible for TRAIN)
2. Previous radiotherapy to the pelvis
3. Previous intravesical therapy
4. Poor bladder function (IPSS >16)
5. A recent or current other cancer. Current non-melanoma skin cancer, cervical carcinoma in situ or localized prostate cancer not requiring current treatment are permissible, as is a history of a separate other malignancy having completed all active treatment ≥2 years previously and without evidence of relapse
6. Pre-existing medical conditions that preclude treatment options in either trial arm
7. Patient currently recruited to another interventional trial or participation within an interventional clinical trial within 3 months of the point of registration within TRAIN.
8. Pregnant or breast-feeding
9. Not able to use appropriate adequate effective contraception during and for up to 6 months after the study (see section 7.4.3)
10. Hypersensitivity to the IMPs or any of their excipients (see relevant SmPC)
11. Any other contraindications to treatment with the study IMPs as per their approved SmPCs

5 TRIAL PROCEDURES

5.1 RECRUITMENT

Patients will be identified from the Urology Specialist MDTs. Patients must have a biopsy-proven high-risk NMIBC (T1G3 or CIS with no evidence of invasive disease).

All participating centres will be required to keep a detailed screening log of all patients with non-muscle invasive bladder cancer who are considered for radical radiotherapy. This log will capture the following information:

- Date patient identified
- Patient initials and year of birth
- Number of patients considered/approached/accepting/declining participation/ineligible
- Screening outcome

- Trial ID (if applicable)
- Reasons for ineligibility / not approaching / declining as applicable

This information will be used to monitor recruitment activity. No patient identifiable data will be collected at this stage.

5.2 SCREENING PROCEDURES

Each patient must have signed and dated an informed consent form prior to screening and before engaging in any trial related procedure. All screening evaluations must be complete before the patient is randomised to a trial treatment.

The following screening procedures must be carried out up to 28 days prior to randomisation, unless otherwise indicated:

- Informed consent
- Medical history
- Cystoscopy* (+/- TURBT and biopsy as required)
- ECOG performance status
- Physical exam and vital signs
- Eligibility criteria
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium)
- Haematology including Full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelets counts
- Concomitant medication record
- CT Urogram**

*Screening cystoscopy can be carried out within 6 weeks prior to randomisation.

**Urogram may be carried out within 3 months prior to randomisation.

5.2.1 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently assigned to trial treatment. Patients who are approached and decline or fail screening will have their initials, year of birth and reasons for not entering the trial recorded on the trial screening log (see section 5.1). The screening log should be emailed to the SCTU trial specific email address monthly. This set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

5.3 REGISTRATION AND RANDOMISATION PROCEDURES

5.3.1 Registration

Eligible patients will be registered on a trial-specific RAVE database, which will automatically generate a trial ID.

5.3.2 Randomisation

Once patients have given written informed consent, they will undergo screening and baseline procedures as required within 28 days prior to randomisation (unless otherwise specified). Providing all relevant inclusion/exclusion criteria have been met, patients will be entered on the trial specific Medidata RAVE database and will then proceed to randomisation. Randomisation will be completed by site staff via a separate web-based system set up by SCTU. Participants will be randomised 1:1 using permuted blocks, stratified by known prognostic factors including disease stage (presence of T1 at randomisation – yes/no) and age (age<70 years and age≥70 years). These stratification factors were considered to be the key predictors of the primary outcome. Treatment should be initiated within 4 weeks following randomisation. If planned treatment timelines fall outside this window, the SCTU should be contacted for advice prior to randomisation.

Please refer to (TRAIN Randomisation Guidance document) for guidance on how to randomise patients.

5.4 TRIAL PROCEDURES

The following assessments are carried out:

Screening Pre-randomisation assessments

- Medical history and examination
- Cystoscopy (+/- TURBT and biopsy as required)
- Full blood count, urea and electrolytes
- LFTs & bone profile
- ECOG performance status
- Physical exam and vital signs
- Urine cytology
- Pregnacy test

Baseline Pre-randomisation assessments

- IPSS, EQ-5D, EORTC QLQ-C30 and QLQ-NMIBC24 questionnaires
- Collect diagnostic tumour block, translational blood and urine sample (after randomisation)

Follow-up assessments – from initiation of treatment

Week 2 (+/- 1 weeks)

- FBC
- U&E
- LFT
- Bone profile
- Review/reporting of participant AEs/SAEs (CTCAE v5.0)
- ECOG performance status
- Physical exam and vital signs

Week 4 (+/- 1 weeks)

- FBC
- U&E
- LFT
- Bone profile
- Review/reporting of participant AEs/SAEs (CTCAE v5.0)
- ECOG performance status
- Physical exam and vital signs

Week 12 (+/- 4 weeks)

- Cystoscopy (+/- TURBT and biopsy as required)
- Urine cytology
- Review/reporting of participant AEs/SAEs (CTCAE v5.0)
- IPSS, EQ-5D, EORTC QLQ-C30 and QLQ-NMIBC24 questionnaires
- Collect translational blood and urine sample
- ECOG performance status
- Physical exam and vital signs

Week 24 (+/- 4 weeks)
- Cystoscopy (+/- TURBT and biopsy as required)
- Urine cytology
- RTOG late morbidity score
- Review/reporting of participant AEs/SAEs (CTCAE v5.0)
- IPSS, EQ-5D, EORTC QLQ-C30 and QLQ-NMIBC24 questionnaires
- HE (ModRUM) questionnaire
- Collect translational blood and urine sample
- ECOG performance status
- Physical exam and vital signs

Weeks 36, 48, 60, 72 and 84 (+/- 4 weeks)
- Cystoscopy (+/- TURBT and biopsy as required)
- Urine cytology
- RTOG late morbidity score
- Review/reporting of participant AEs/SAEs (CTCAE v5.0)
- IPSS, EQ-5D, EORTC QLQ-C30 and QLQ-NMIBC24 questionnaires
- ECOG performance status
- Physical exam and vital signs

Additional procedures at week 48 only
- FBC
- U&E
- LFTs and bone profile

Week 96 (+/- 4 weeks)
- FBC
- U&E
- LFTs and bone profile
- Cystoscopy (+/- TURBT and biopsy as required)
- CT Urogram
- Urine cytology
- RTOG late morbidity score
- Review/reporting of participant AEs/SAEs (CTCAE v5.0)
- IPSS, EQ-5D, EORTC QLQ-C30 and QLQ-NMIBC24 questionnaires
- ECOG performance status
- Physical exam and vital signs

Note: the cystoscopy can be local anaesthetic flexible cystoscopy, as per clinical preference.

5.5 EXTENDED FOLLOW UP

Follow up 6-monthly (+/- 4 weeks) to end of trial
- Cystoscopy (+/- TURBT and biopsy as required)

- Urine cytology
- Concomitant medication
- CTCAE grade
- RTOG late morbidity score
- IPSS
- Survival status
- ECOG performance status
- Physical exam and vital signs

Note: the cystoscopy can be local anaesthetic flexible cystoscopy, as per clinical preference.

When follow-up in the trial is anticipated to be close to completion, a final round of data collection will be carried out to ensure that survival information is up-to-date.

5.6 FOLLOWING RECURRENCE OR PROGRESSION

Once a participant is observed to have had recurrence or progression, they should revert to a simplified follow-up process. The following information should be captured following progression/recurrence:

- Staging of recurrence
- IPSS
- Capacity of bladder (if undergoing general anaesthetic)
- Site of biopsy

Translational bloods and urine should be taken ideally as soon as diagnosis is made but can be taken within +/- 4 weeks from recurrence or progression. In addition, the following should be reviewed and recorded every 6 months (+/- 4 weeks) until the end of the study:

- Subsequent treatment(s) related to cancer
- Response to further treatment(s)
- Occurrence of:
    - Cystectomy
    - Metastatic disease
- Survival status

5.7 TRIAL INTERVENTION DISCONTINUATION

In consenting to the trial, patients have consented to the trial treatment, follow-up, and data collection. Patients may be discontinued from the trial treatment at any time. If the patient discontinues the trial treatment or a Principal Investigator discontinues a patient from the trial treatment for medical reasons, the patient will continue to be followed up per protocol unless they withdraw consent.

A patient may withdraw, or be withdrawn, from trial treatment for the following reasons:

- Clinical decision
- Patient's choice
- Completion of treatment
- Progression/recurrence
- Pregnancy
- Termination of the trial by Sponsor

Full details of the reason for trial treatment discontinuation must be recorded in the eCRF and patient's medical record.

5.7.1 Trial Withdrawal

The patient is free to withdraw consent from the trial at any time, without providing a reason, and without their medical care or legal rights being adversely affected.

Investigators should explain to patients the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, patients who have withdrawn from the trial treatment should continue to be followed up per protocol. If patients additionally withdraw consent for this, they should revert to standard clinical care/follow-up as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect any routine data (i.e., data that can be collected with no impact on the patient beyond standard clinical care/follow-up), and this will continue unless the patient explicitly requests otherwise. If this is requested, this constitutes complete withdrawal from the trial and should be recorded as end of trial for the patient in the relevant eCRF and in their medical record, and no further data should be collected for this patient.

5.8 DEFINITION OF END OF TRIAL

Last patient, last visit is anticipated to be at two years following the last participant randomised. If the number of events required by the sample size calculation has been met at this point, the trial will end when all trial data has been entered and cleaned (as far as possible, in agreement with the CI and trial team) and the database has been locked. If the number of events has not been met, the trial team, in agreement with the Trial Steering Committee, may delay database lock to allow for further events to accrue to achieve the targeted power. Once the number of events is met, end of trial will be declared as above.

5.9 STORAGE AND ANALYSIS OF CLINICAL SAMPLES

Please see the TRAIN lab manual for details of storage and analysis of translational samples taken during the trial period.

6 TRIAL TREATMENTS

The trial will randomly allocate patients equally between the standard of care (BCG) and radiotherapy with a radiosensitiser with a post-treatment study follow-up period up to 24 months.

6.1 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Within the trial, the following are classed as IMPs:
• BCG
Radiosensitisers:
• Gemcitabine 75-100mg/m^2
• 5-FU and Mitomycin C - Fluorouracil 500mg/m^2 and Mitomycin C 12mg/m^2
• Carbogen and nicotinamide (CON) - 2% CO^2 and 98% O^2Carbogen breathing and oral nicotinamide 40-60mg/kg

All IMPs will be prescribed from hospital stock and by active substance – the trial does not require sites to use any particular brand name drug.

The dosing regimen for the IMPs is based on the NICE bladder cancer guidance (2015) and the BCON phase III randomised controlled trial (Hoskin et al. JCO 2010).

6.2 REGULATORY STATUS OF THE DRUG

TRAIN is classified as a Type A trial (risk no higher than standard care) because although the drugs/IMPs are not licensed for use as radiosensitisers, the use is established practice.

6.3 PRODUCT CHARACTERISTICS

Name of Product	SmPC	Section	Manufacturer	Last updated 21-Oct-2025
BCG	SmPC	4.8	Merck Sharp & Dohme (UK) Limited	10-Feb-2021
Gemcitabine 75-100mg/m^2	SmPC	4.8	Ranbaxy (UK) Limited a Sun Pharmaceutical Company	22 Mar 2024
Fluorouracil 500mg/m^2	SmPC	4.8	Hospira UK Ltd	20 Jan 2025
Mitomycin C 12mg/m^2	SmPC	4.8	Vygoris Limited	06 Dec 2024
2% CO^2 and 98% O^2Carbogen breathing	Gas Data Sheet	4.4 – 4.9	BOC	11 May 2022
Nicotinamide 40-60mg/kg	SmPC	4.8	TEOFARMA S.R.L	02 Nov 2017

These IMP's SmPC are given as a guidance for RSI. As the IMP's will be supplied via local hospital stock, hospital sites can use the brands they current use, even if they differ from the information listed in the table above.

6.4 INVESTIGATIONAL MEDICINAL PRODUCT(S) SUPPLY

6.4.1 Drug Storage and Supply

All IMP stock will be taken from current hospital stock located at site and stored according to their SmPC and local hospital guidelines. The pharmacy team at site will be responsible for ensuring the correct storage and sufficient stocks of the IMP at site.

6.5 CONTROL ARM

Patients in the control arm will receive standard of care BCG treatment protocol for up to 36 months. As noted in the rationale for the trial, BCG supply can be unpredictable. The following provides guidance for when there is either limited or no supply of BCG:

- **Limited supply**: give induction BCG up to 2nd batch of 3 doses of maintenance BCG. Following induction and up to 2nd batch of 3 doses of maintenance BCG therapy, offer (assisted) mitomycin C chemotherapy, or alternative maintenance intravesical chemotherapy (e.g., epirubicin); or consider induction treatment with intravesical gemcitabine chemotherapy.
- **No supply**: consider induction and maintenance therapy with (assisted) mitomycin C chemotherapy; or consider induction treatment with intravesical gemcitabine chemotherapy.

6.6 EXPERIMENTAL ARM

Patients randomised to the radiotherapy arm will receive a hypofractionated schedule of external beam radiotherapy with a regimen of 55Gy in 20 fractions given once daily Monday to Friday over 4 weeks. Radiotherapy will be delivered with a conventional or 3D conformal technique with an empty bladder. It will be administered concurrently with a radiosensitiser (detailed below) selected by the treating physician according to local institutional practice. For patients randomised to receive radiotherapy, treatment should commence less than 4 weeks following randomisation, to align with the control arm. TRAIN Radiotherapy Planning and Delivery Guidelines are to be followed. Any deviations from the RT Planning and Delivery Guidelines are to be recorded in the source data and reported to SCTU.

Radiosensitiser will be selected as one option from the following:

• Gemcitabine 75-100mg/m^2 administered once a week during a four-week radiotherapy course. Cycle 1 will be given on the first radiotherapy day, to a planned total of 4 cycles. 2–4 hours prior to radiotherapy
• 5-FU and Mitomycin C - Fluorouracil 500mg/m^2 Days 1-5 and 16-20 via continuous infusion. Mitomycin C 12mg/m2 Day 1 via intravenous infusion
• Carbogen and nicotinamide (CON) - 2% CO^2 and 98% O^2 Carbogen will be delivered through a closed breathing system with an expansion bag and one-way valve. Either an airtight face mask or mouthpiece with nasal clip will be used to deliver the carbogen. Carbogen breathing will be started 5 minutes prior to the delivery of radiation. Carbogen breathing will continue daily with each fraction of radiotherapy. Oral nicotinamide of 40-60mg/kg will be taken 1.5 to 2 hours before radiotherapy.

Centres should aim to use the same regimen for all patients receiving radiosensitising treatment throughout the trial. If the patient isn't fit for the centre's usual radiosensitising treatment an alternative may be substituted after discussion with the TRAIN trial manager.

6.6.1 Rational and Labelling of Investigational Medicinal Product(s)

In this trial the radiosensitising drugs are considered an IMP; however, these drugs are used routinely in hospitals for MIBC. Clinical labels are therefore not needed for the IMPs, however your labels must include information from Annex 13 point 26 https://health.ec.europa.eu/system/files/2016-11/2009_06_annex13_0.pdf and in accordance with the relevant GMP guidelines.

6.6.2 Accountability

The pharmacy team at site are responsible to ensure all accountability documents for the dispensing and destuction of the IMP's according to local SOPs and SmPCs.

6.7 TREATMENT SCHEDULE

6.7.1 NHS Standard of Care BCG

A standard protocol of 6 weekly intravesical installations, followed by 3 weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months (depending on toxicity). In the event of BCG shortage, please refer to Section 6.5.

6.7.2 Radiotherapy Quality Assurance

The radiotherapy quality assurance programme for the trial will be co-ordinated by the National Radiotherapy Trials Quality Assurance (RTTQA) Group. Details of the programme can be found at the RTTQA website (www.rttrialsqa.org.uk). As part of the radiotherapy quality assurance, a separate Radiotherapy Planning and Delivery Guidelines document will detail the QA programme for the trial. Please refer to this document for-specific radiotherapy and quality assurance details. Any deviations from the RT Planning and Delivery Guidelines are to be recorded in the source data and reported to SCTU.

Prior to site activation, sites will be asked to complete the following:

- Facility Questionnaire
- Dosimetry Audit
- Dummy Run

Ongoing trial requirements:
At least the first patient recruited from each site will be subject to retrospective review. Further prospective and/or timely retrospective reviews may be deemed necessary at the discretion of the RTTQA group and the trial Chief Investigator (CI). The reviews will be led by the RTTQA Group to ensure adherence to the trial RT Planning and Delivery Guidelines and the protocol. Non-compliance will be highlighted to the CI, local PIs and the Trial Management Group by the RTTQA Group and a decision will be made regarding further action for the patient and future patients recruited at that site.

All data will be anonymised prior to being sent for review.

6.8 DOSE DELAYS AND MODIFICATIONS FOR TOXICITY

BCG

- Therapy should be delayed in patients with a confirmed/suspected urinary tract infection (urine dipstick test and subsequent positive urine culture result). Treatment can be resumed once the urine culture becomes negative and antibiotics or antiseptic treatment has been stopped for at least 24h.
- Therapy must be delayed for gross haematuria and postponed until the haematuria has been successfully treated or has resolved.

Radiotherapy

Delays and treatment gaps should be avoided, however if gaps occur please refer to the TRAIN Radiotherapy Planning and Delivery guidelines for further information. If any issues arise during TRAIN participants' treatment, SCTU and the RTTQA team should be contacted in real time for guidance.

Radiosensitisers
Pharmacy and site staff should refer to the IMP's SmPC section 4 for specific reactions.

6.9 KNOWN DRUG REACTIONS AND INTERACTION WITH OTHER THERAPIES

Pharmacy and site staff should refer to the IMP's SmPC section 4 for specific reactions.

6.10 CONCOMITANT MEDICATIONS

Information on any treatment received by the participant, along with dose, frequency and therapeutic indication, will be recorded in the electronic case report form (eCRF). The period of reporting will start from when the participant signs the informed consent form until the end of the trial.

The following is prohibited for all trial participants:

- Any investigational drug (also for indications different to anticancer therapy)
- For participants administered 5-Fluorouracil, the following are contraindications with 5-FU and must be prohibited for participants being administered 5-FU: previous treatment with brivudine, sorivudine or their chemically related analogues
- Any other medication contraindicated as per SmPC of all IMPs must be listed

6.11 TRIAL RESTRICTIONS

Participants should follow the contraception requirements listed in section 7.4.3.

7 SAFETY

7.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the Sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*
Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). *When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected. Reports which add significant information on specificity or severity of a known documented adverse event are to be considered unexpected.*

Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that at any dose: • Results in death • Is life-threatening* • Requires hospitalisation, or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly or birth defect • Important medical events*** *'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE. ***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A Serious Adverse Reaction, the nature and severity of which is not consistent with the information about the medicinal product in question as set out in the Reference Safety Information.

7.2 TRIAL SPECIFIC REQUIREMENTS

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the **National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0** should be used. This is available online at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Severity grade of each adverse event must be determined by using the unique clinical descriptions of severity for each AE in NCI CTCAE v5.0.

All adverse events should be recorded in the TRAIN eCRF. Each time there is a change in grade of an adverse event this should be recorded on a separate log line on the adverse event form on the eCRF. Refer to eCRF guidance document for further information on how to record these.

All Adverse Events (AEs) should be reported on the AE eCRF.

Reporting of all safety event will start from when the participate signs the consent form until the end of study.

7.2.1 Seriousness

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

All reportable adverse events that fulfil the criteria definition of 'serious' in protocol section 7.1, must be reported to SCTU using the Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

7.2.2 Exceptions

For the purposes of this trial, the following **SAEs do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Death due to high risk NMIBC
- NMIBC disease progression
- Hospitalisations for elective treatment of a pre-existing condition (the pre-existing condition needs to have been captured within the medical history CRF)
- SAEs listed as expected events (see section 7.4)
- SAEs between consent and randomisation that are not trial related

In addition to the definition above, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. Elevations in liver biochemistry that meet Hy's Law criteria are reported as SAEs, using the important medical event serious criterion if no other criteria are applicable.

BCG intravesical therapy may cause tuberculin sensitivity in those with previous history of TB, hence such patients should not receive this treatment. BCG intravesical therapy can also cause a tuberculous-like infection called BCG sepsis, which would require treatment with anti-TB medication. The latter risk is rare.

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the MHRA will be informed of both parties' points of view.

Relationship	Description	Denoted
Unrelated	There is no evidence of any causal relationship	SAE
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 participant's clinical condition, other concomitant treatment).	SAE
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 participant's clinical condition, other concomitant treatments).	SAR/ SUSAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/ SUSAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/ SUSAR

7.3 EXPECTEDNESS

Both early and late toxicity will be recorded using NCI CTCAE Version 5.0. These will include assessments of bladder, bowel, skin and renal/ureteric toxicity and general/systemic symptoms.

Expected events for BCG:

Organ	Expected events
Bladder	Urinary incontinence Micturition urgency Cystitis Dysuria Pollakiuria Haematuria
Gastrointestinal	Diarrhoea Nausea Vomiting Abdominal pain
Blood and lymphatic system	Anaemia
Musculoskeletal and connective tissue	Arthralgia Arthritis Myalgia
Respiratory, thoracic and mediastinal	Pneumonitis
General/systemic	Fatigue Influenza-like illness Pyrexia Malaise Rigors

Early toxicity is defined as side effects occurring within 90 days of RT. Late side effects are those occurring after 90 days or persisting beyond this time.

Expectedness assessments for bladder radiotherapy are made against the list of expected events in the table below.

Expected events for radiotherapy:

Organ	Expected events

Bladder	Urinary urgency and frequency Dysuria Nocturia Haematuria
Bowel	Looser stools Abdominal discomfort Tenesmus Mucus or blood in the stool
Skin	Erythema/discoloration Desquamation Soreness
General/systemic	Fatigue

Addition expected events from RT treatment may relate to the choice of radiosensitiser selected as per the table below:

Radiosensitiser	Expected events
Chemotherapy (Gemcitabine, 5-FU or mitomycin-C)	Myelosuppression, nausea and vomiting, flu-like symptoms, asthenia, derangement in LFTs, mucositis, change in bowel habit (diarrhoea or constipation), palmar-planter erythrodysesthesia
Carbogen and Nicotinamide	Sensation of breathlessness, headache, dizziness/light-headedness, anxiety, tachycardia, changes in blood pressure, nausea, flushing, loose bowels

Late toxicity events from RT may include:

- Urinary- persistent haematuria, urinary frequency, urinary incontinence, urinary fistulae
- Gastrointestinal- chronic diarrhoea, tenesmus, faecal incontinence, rectal fistulae
- Metabolic- pelvic osteoporosis
- General/systemic- fatigue, malaise, vitamin B12 deficiency
- Sexual dysfunction- erectile dysfunction, vaginal stenosis/atrophy, dyspareunia, early menopause, sub-/in-fertility
- Peripheral lymphoedema- affecting the lower limbs
- Secondary malignancies

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available, then the AE should be recorded as 'unexpected'.

Expectedness assessments are made against the approved Reference Safety Information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product	**SmPC**	**Section /Table No.**	**Manufacturer**	**Last updated on eMC** DD-MMM-YYYY
Gemcitabine 75-100mg/m^2	SmPC	Section 4	Sun Pharmaceutical industries Europe	22-Mar-2024
Fluorouracil 500mg/m^2	SmPC	Section 4	Hospira UK Limited	20-Feb-2025
Mitomycin C 12mg/m^2	SmPC	Section 4	Sun Pharmaceutical industries Europe	06-Dec-2024
2% CO^2 and 98% O^2Carbogen breathing	BOC sheet	Section 4	BOC Limited	11-May-2022

Nicotinamide 40-60mg/kg	SmPC	Section 4	TEOFARMA S.R.L	02 Nov 2017
BCG	SmPC	Section 4	Merck Sharp & Dohme (UK) Limited	10-Feb-2021

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

As per standard practice, for the nIMPs in this trial please assess expectedness against the most up to date SmPC in place at the time of the event.

7.4 REPORTING PROCEDURES

Any questions concerning adverse event reporting should be directed to the SCTU in the first instance.

7.4.1 Reporting Details

7.4.1.1 Adverse Events

All reportable AEs should be recorded on the eCRF as per the trial specific requirements listed in Section 7.2.

7.4.1.2 Serious Adverse Events

For all reportable SAEs, an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

Or Contact SCTU by phone for advice and then email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the grading system referenced in section 7.2 i.e. the NCI CTCAE v5.

Additional information should be provided as soon as possible as it is received if all information was not included at the time of reporting.

7.4.1.3 Reporting Timelines

All protocol reportable AEs and SAEs should be reported from consent up to the end of the follow-up period (not including the remote survival status follow-up). Between consent and randomisation only AEs and SAEs that are trial related should be reported.

All unresolved adverse events should be followed by the investigator until resolved or one of the ends of trial criteria is met (i.e., lost to follow up, withdrawal etc.). At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial Sponsor of any death or adverse event occurring at any time after a patient has discontinued or terminated trial participation that may reasonably be related to this trial.

7.4.2 Pre-existing Conditions

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions worsen during the trial. The condition, however, must be reported on the Medical History eCRF. Any AEs which occur after informed consent should be recorded on the AE eCRF as per safety reporting section. AEs between consent and randomisation only need reporting if they are trial related.

7.4.3 Contraception and Pregnancy

For the purposes of this trial, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. For the purposes of this trial, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Female patients of childbearing potential must agree to use a form of highly effective contraception from when they consent to join the trial (prior to any treatment) and until at least 6 months after the end of the study.
Contraception that is considered highly effective is as follows:

- Combined hormonal contraception associated with inhibition of ovulation
    - Oral
    - Intravaginal
    - Transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- True sexual abstinence (see below)

Male patients with partners of childbearing potential must agree to use a condom from when they consent to join the trial (prior to any treatment), during the treatment period and until 6 months after the end of the trial.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

If a patient becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to radiotherapy or the NIMP, the investigator must ensure that the patient and the patient's healthcare professional are aware that follow up information is required on the outcome of the pregnancy.

Follow-up is of course, dependent on obtaining informed consent for this from the patient. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information should be collected.

The investigator must immediately notify SCTU of this event via the Pregnancy Notification Form in accordance with SAE reporting procedures.

Protocol-required procedures for trial discontinuation and follow-up must be completed.

If the patient leaves the area, their new healthcare professional should also be informed.

Contraception requirements are adequate for the IMPs used in TRAIN and in compliance with CTCG guidance.

7.4.4 Overdose

Pharmacy and clinical site teams will refer to IMP's SmPC for overdose guidelines. Pharmacy and clinical staff teams must follow local SOP and guidelines. Any overdose must be notified to Sponsor (via the trial inbox) with overdose reason and outcome, as soon as possible. If an SAE is associated with the overdose, ensure the overdose is fully described in the SAE report form.

7.5 RESPONSIBILITIES

7.5.1 Principal Investigator (PI)

The PI, or medically qualified doctor who is registered on the delegation of responsibility log, is responsible for:

1. Using medical judgement in assigning seriousness, causality and whether if requested, the event/reaction was anticipated (in line with the expectedness information) approved for the trial.
2. Ensuring that all SAEs are recorded and reported to the SCTU immediately, or at a least within 24 hours, of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with the SCTU if a record of receipt is not received within 1 working day of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the SCTU in line with the requirements of the protocol.

7.5.2 Chief Investigator (CI) / delegate or independent clinical reviewer:

The CI, or delegated clinical reviewer, is responsible for:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether if requested, the event was anticipated (in line with the expectedness information) where it is required as a second clinical opinion or if it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

5. Upon request review Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and reviewing the Development Safety Update Report (DSUR).

7.5.3 Sponsor / delegate

The Sponsor, or delegate, is responsible for:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Checking causally related events against the approved RSI, in place at time of event onset.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Ensuring that expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC are within the required timelines.
6. Notifying Investigators of SUSARs that occur within the trial.
7. Regularly checking for and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.
9. All amendments will be authorised by Sponsor prior to submission.

7.6 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and REC of the measures taken and the circumstances giving rise to those measures.

7.7 DEVELOPMENT SAFETY UPDATE REPORTS (DSUR)

The Sponsor, or delegate, will provide DSURs once a year throughout the trial, or as necessary, to the Competent Authority (the MHRA in the UK), and the appropriate REC.

The report will be submitted within 60 days of the Development International Birth Date of the trial each year until the trial is declared ended.

8 STATISTICS AND DATA ANALYSES

8.1 METHOD OF RANDOMISATION

Randomisation will be undertaken through Southampton CTU (SCTU) via ALEA, an Interactive Web-based Response System. Participants will be randomised 1:1 using permuted blocks, stratified by known prognostic factors, disease stage (presence of T1 at randomisation – yes/no) and age at randomisation(age<70 years and age≥70 years). These stratification factors were considered to be the key predictors of the primary outcome. Participants will have TURBT, then within 6 weeks patients will be randomised and start their trial treatment.

8.2 SAMPLE SIZE

The sample size was calculated using the *rpact* package in R for group sequential designs, using alpha = 0.025 (one-sided), power = 0.9 (with O'Brien-Fleming boundaries to control type II error), hazard ratio = 0.5, and a piecewise exponential survival distribution with event rate in the control arm of 10, 20, 25 and 30% at 3, 6,

12 and 24 months. With accrual time of 36 months and minimum follow-up time of 24 months, the required sample size is 312 patients (90 events). Accounting for 5% drop out, the final sample size is 328. The sample size calculation accounts for an interim analysis for futility.

8.3 INTERIM ANALYSIS

The interim analysis is designed to take place after 50% of the information in the outcome is collected (i.e., 45 events); this is anticipated to take place just under 2.5 years into recruitment with 249 participants. This approach leads to a probability of 0.60 that the study will stop if the true hazard ratio is 1, and a probability of 0.02 if the true hazard ratio is 0.5. The study will stop if the observed hazard ratio (calculated by a Cox proportional hazard model and adjusted for stratification factors) is greater than 0.924.

8.4 STATISTICAL ANALYSIS PLAN (SAP)

A detailed statistical analysis plan will be developed prior to database lock, and all data and appropriate documentation will be stored for a minimum of 25 years after the completion of the trial.

Primary Analysis

The primary analysis will use a Cox proportional hazards model to calculate a hazard ratio, 95% confidence interval and p-value for group allocation, adjusted for stratification factors disease stage (presence of T1 at randomisation – yes/no) and age at randomisation. Not starting treatment, treatment delays, and missed treatment will be handled under the treatment policy strategy (per the ICH-E9 estimands framework) [31], meaning participants experiencing these events will be included in the analysis according to their group allocation. Sensitivity analyses will be considered in cases where cystoscopies are not carried out or carried out outside of protocol defined windows.

Should BCG supply impact the trial and nationally agreed protocols for BCG shortage initiated [36], a supplementary analysis will be undertaken to target the estimand of treatment effect under the hypothetical situation of no BCG shortage. This will use multiple imputation to impute outcomes for those affected (applying rules of thumb relating to missing data, where very low (<5%) or high (>40%) rates might suggest this approach is unlikely to be beneficial/appropriate [37]). As lack of BCG availability is unlikely to be related to the participant, the assumption of missing at random is likely to be a reasonable assumption.

Results from the Cox model will be presented alongside Kaplan-Meier curves and estimates of event-free survival at 12 and 24 months.

An interim analysis for futility will take place when 50% of the information in the outcome is collected (i.e., approximately 45 events); this is anticipated to take place just under 2.5 years into recruitment with 249 participants. This analysis targets the same estimand as the primary analysis and will therefore apply the same methods for handling intercurrent events as described above. Data entry, data cleaning and analysis will commence imminently after 45 events are observed. During this time, we will continue to recruit patients.

Secondary analyses

Although recurrence is anticipated to constitute the vast majority of events, a longitudinal analysis using an ordinal scale (event-free, recurrence, progression, cystectomy, metastases, death) will be considered if there is a high number of non-recurrence related events to account for the ordering of severity in events. Time-to-event outcomes that are constituent parts of the primary outcome will be evaluated in the same way as the primary analysis. Treatment fidelity, including treatment delays, missed treatment, not starting treatment and completed treatment will be reported by arm. Questionnaire data will be summarised by group and timepoint. All adverse events and serious adverse events occurring post-randomisation will be summarised by system/organ class and term (MedDRA), with grade (CTCAE v5.0). SAEs will be listed.

Subgroup analyses

We will describe event-free survival across the different radiosensitisers, and for CIS versus T1G3 disease. A forest plot will be used to describe treatment effects across centres.

8.4.1 Primary endpoint

Event-free survival between treatment arms defined as time from randomisation to any of: CIS or high-risk G3 non-muscle invasive papillary tumour recurrence, continued presence of HR NMIBC even after treatment completion, progression to muscle-invasive disease, distant metastatic bladder cancer, cystectomy (for any reason) or death from any cause. Patients will be censored at the point of last follow-up where an event has not occurred. Cystoscopies will be every 3 months as per standard of care and in accordance with NICE guidelines to capture progression and recurrence data.

8.4.2 Secondary endpoints

- Recurrence-free survival – defined as time from randomisation to recurrence of non-muscle invasive papillary tumour. Patients are censored at the last follow-up if event free.
- Cancer specific survival – defined as time from randomisation to death from cancer. Patients who die of a cause other than the cancer under study or who are lost to follow-up are 'censored' at the last date on which they were known to be alive.
- Cystectomy-free survival – defined as time from randomisation to cystectomy. Patients are censored at the last follow-up if event free.
- Progression-free survival – defined as time from randomisation to progression to muscle-invasive disease. Patients are censored at the last follow-up if event free.
- Metastasis-free survival (MFS) – defined as time from randomisation to progression to distant metastatic bladder cancer. Patients are censored at the last follow-up if event free.
- Overall survival – defined as time from randomisation to death due to any cause. Patients are censored at the last follow-up if event free
- Treatment fidelity – defined as how well each group implemented treatment as intended
- Adverse events (CTCAEv5.0)
- Cost-effectiveness
- Toxicity – acute toxicity will be assessed weekly and at 6 weeks following treatment completion using clinician reported acute toxicity (CTCAE v5.0). Late toxicity will be assessed at 6 and 12 months after treatment completion and annually thereafter using CTCAE v5.0.
- Questionnaires will be scored according to relevant scoring systems.

9 HEALTH ECONOMICS

The economic analysis will include: i) a within-trial cost effectiveness to compare the costs and health outcomes (QALYs) accrued over the follow up period for patients in the intervention and control arms; and ii) development of a cost-effectiveness model to extrapolate cost and QALY estimates over a longer time horizon. The analyses will follow the recommended methods and 'reference case' recommended by NICE [33], including: an NHS and Personal Social Services perspective for costing; estimation of QALYs using EQ-5D data and UK value sets, and discounting of costs and QALYs at 3.5% per year.

9.1 WITHIN-TRIAL ECONOMIC ANALYSIS

A within-trial cost effectiveness analysis will be conducted. Costs and QALYs will be calculated for the two treatment arms and compared. Net costs will include direct treatment costs (e.g. medication, staff time for unscheduled health care visits and hospital admission costs), and adverse event costs and these data will be collected in the trial. Information on patients' use of health and social services that might be related to cancer care or treatment will be taken from a patient questionnaire administered at follow up. Individual costs will then be calculated, using unit costs for resource items obtained from routine national sources, including NHS Reference Costs and the PSSRU Unit Costs of Health and Social Care [34]. Health-related quality of life (EQ-

5D utility scores) will be calculated at baseline and all follow-up points. EQ-5D 5L utility scores will be mapped to EQ-5D 3L utility scores, as recommended by NICE. QALYs will be calculated from EQ-5D and mortality data, using the 'area under the curve' method. For patients who die during the trial, utility is set to zero from the date of death. We will conduct multiple imputation for missing data with adjustment for baseline co-variates. Results will be presented as a ratio of incremental cost per QALY gained. Non-parametric bootstrapping will be used to obtain estimates of joint uncertainty over mean costs and QALYs, which will be represented by a scatterplot on the cost-effectiveness plane, and as a cost effectiveness acceptability curve (CEAC) – showing the probability that radiotherapy with radiosensitisation is cost effective.

9.2 ECONOMIC MODELLING

We will conduct a targeted literature search to find related NICE technology appraisals and published economic evaluations. These will be reviewed to inform the model design and sources of evidence. Modelling will be conducted according to NICE guidelines. The model will probably take the form of a Markov-type health state transition model, as used in previous studies in non-muscle invasive bladder cancer by Mossanen et al. and Sharma et al [35]. Health states that describe the disease process are likely to include disease-free, disease recurrence, progression and death. The model design will be discussed and agreed with members of the project team and other experts. The time horizon of the model will be 20 years and we will conduct scenario analyses with different time horizons. Input parameters will be estimated from the trial data, supplemented by evidence from the literature when necessary. Targeted search methods will be used to identify best-available sources of evidence. As with the within-trial analysis, results will be presented as an incremental cost effectiveness ratio, and with a cost-effectiveness scatterplot and CEAC curve. Uncertainty will be explored with deterministic and probabilistic sensitivity analysis. In addition, uncertainties relating to model structure or choice of data sources will be explored through scenario analysis. Validity of the model will be assessed by a health economist not involved in its development. This will include tests of internal validity: checks that input parameters match specified sources and inspection of coding (white box validation); stress testing of model behaviour (black box validation); and comparison of modelled event rates during the trial follow-up period with trial observations. External validity will be assessed by comparison of model results with relevant estimates from the literature.

10 TRANSLATIONAL RESEARCH

Sites will be provided with a TRAIN Trial Laboratory Manual for a detailed description of sample collection, handling and shipment processes. A 'TRAIN Translational Samples Dispatch Log' needs to be maintained for each patient documenting the collection, storage and shipment of translational samples.

The TRAIN-gen study

The TRAIN patients' biospecimens will contribute to the TRAIN-gen programme of translational research, funded by an NIHR i4i Product Development Award (NIHR505393). The objectives of TRAIN-gen are:

- To evaluate whether a proportion of surveillance flexible cystoscopies can be omitted during the follow-up of HR-NMIBC patients by the use of the GALEAS™ Bladder urine test, thereby improving patient quality-of-life and reducing healthcare costs.
- To identify specific subgroups of patients who do/do not respond to BCG and/or radiotherapy, thereby permitting personalised therapy recommendations.

Diagnostic tumour block

Pre-treatment archival biopsy processed as formalin-fixed paraffin-embedded (FFPE) blocks will be collected from all patients where consent has been obtained. Central storage will be at the Manchester Cancer Research Centre HTA licensed Tissue Bank (HTA licence number 30004). From Manchester, FFPE blocks will be transferred by courier to Veracyte Inc (6925 Lusk Boulevard, Suite 200, San Diego, CA 92121, USA) in order to undergo whole transcriptome array analysis for gene expression profiling.

Gene expression profiling allows tumours to be clustered on the basis of tumour biology and gives insight into responses to different therapies: the UROMOL study clustered NMIBCs into 4 subtypes (Class 1, Class 2a, Class 2b, Class 3) with differing clinical outcomes [38]. In other studies, three BCG response subtypes (BRS1/2/3) have been identified in patients with HR-NMIBC, with worse outcomes for patients with BRS3 tumours [39]. In MIBC, a pilot 24-gene hypoxia signature demonstrated independent prognostic and predictive value for patients receiving radiotherapy, identifying patients likely to benefit from the addition of carbogen-nicotinamide [40]. Given overlap in abnormal biological pathways in HR-NMIBC and MIBC [38, 41, 42], we consider that molecular subtypes and/or hypoxia signatures will play a future role in predicting response to BCG and/or radiotherapy in HR-NMIBC patients.

In brief, RNA will be extracted from macrodissected FFPE tissues and genome-wide gene expression analysed using the Decipher Bladder Genomic Subtyping Classifier (GSC) oligonucleotide microarray assay in Veracyte's CAP/CLIA laboratory. We will use binomial regression and Cox proportional hazards models to determine the prognostic and predictive power of UROMOL2021 subtypes and other signatures (hypoxia, BRS) in relation to BCG/radiotherapy responses. We will also develop multimodal models using our established methods [43-45], leveraging clinical, transcriptome, and GALEAS Bladder mutation data.

Blood

All study participants will be asked for translational blood samples. A separate laboratory protocol will be produced to outline the methods in detail. Central storage will be at the Manchester Cancer Research Centre HTA licensed Tissue Bank (HTA licence number 30004).

Any samples remaining once trial analyses are complete will be stored appropriately for future use. Southampton CTU will keep record of the conditions of consent for each patient sample. If a patient does not give consent for their samples to be used outside of the trial or subsequently withdraws consent for their samples to be used, Southampton CTU will inform the relevant central laboratory who will be responsible for destroying the samples and confirming this in writing to Southampton CTU once done.

Urine

All study participants will be asked for translational urine samples. A separate laboratory protocol will be produced to outline the methods in detail. Samples will be sent to Manchester Cancer Research Centre HTA licensed Tissue Bank (HTA licence number 30004), prior to transfer to Nonacus Ltd (Unit 5, Quinton Business Park, 11 Ridgeway, Quinton, Birmingham B32 1AF, UK) for GALEAS™ Bladder testing.

GALEAS Bladder (GB) is one of the multiplex urine markers highlighted by the European Association of Urology (EAU) Guidelines as having *"shown fairly high sensitivities to detect tumour recurrence, particularly in HG (high-grade) disease, along with very high NPVs (negative predictive values) to make the premises for their future implementation in follow-up*". GB was developed by the Bladder Cancer Research Centre [46-49] (BCRC) at the University of Birmingham with Cancer Research UK (CRUK) and Medical Research Council (MRC) funding, and commercialised with Nonacus Ltd (UK, SME); clinical testing is provided by Nonacus Clinical Services (Birmingham, UK). For NMIBC surveillance, GB demonstrates 100% sensitivity for the detection of aggressive early BC (high-grade NMIBC) [49]). We therefore intend to retrospectively investigate whether a proportion of surveillance flexible cystoscopies can be omitted during the follow-up of HR-NMIBC patients by the use of the GALEAS Bladder urine test, thereby improving patient quality-of-life and reducing healthcare costs.

In brief, the test utilises DNA extracted from a 30-50ml urine sample, followed by target capture and error-suppressed ultra-deep sequencing to identify BC-associated somatic mutations in 23 genes (451 single nucleotide variants)[49, 50]. Sequenced genes include: *TERT* (promoter), *FGFR3*, *PIK3CA*, *TP53*, *ERCC2*, *RHOB*, *ERBB2*, *HRAS*, *RXRA*, *ELF3*, *CDKN1A*, *KRAS*, *KDM6A*, *AKT1*, *FBXW7*, *ERBB3*, *SF3B1*, *CTNNB1*, *BRAF*, *C3orf70*, *CREBBP*, *CDKN2A* and *NRAS*. One or more of these mutations are present in 96% of BCs and sufficient DNA is obtained from >95% of urine samples [48]. Test kits are given to patients in clinic or sent to their homes, with urine samples posted to Nonacus Clinical Services (Birmingham) for testing (UKAS Medical Laboratory

Accreditation ISO 15189). A custom bioinformatic pipeline based upon widely-used publicly-available tools identifies cancer-associated variants [50], with detection of one or more variants resulting in a positive test result [49]: https://nonacus.com/clinical-services/galeas-bladder/. GB readouts will be test-positive/negative, the genes mutated, and their variant allele frequencies, VAF – the percentage of mutant DNA within all of the DNA (normal and mutant) in the sample.

To understand if GB could be used to reduce the frequency of cystoscopy in the group who are double-negative at 3-months (negative by cystoscopy and by BG testing), we will assess the pattern of events over time. We will estimate the proportion of this group who remain event-free at each follow-up time (primarily months 6-24, where cystoscopy occurs 3-monthly). This will be supported by a Kaplan-Meier plot (including the other groups defined by the combination of their cystoscopy and GB result) and 95% confidence interval (CI). As most events are anticipated to occur within the first 6-months, we will repeat the above analyses in those who are double-negative at 6 months (anticipated to be n=161). Based on the sample size calculations for TRAIN and information on GB test performance, we anticipate n=176 participants to be double-negative at 3-months (90% event-free by cystoscopy, of which 63% are also negative by GB). Assuming that the double-negative group have a hazard rate half that of the non-negative group, we anticipate 15, 19 and 22 events by 6, 9 and 12m respectively. These figures provide lower 95% one-sided Wilson CIs of 0.87, 0.85 and 0.83 for the proportion who are event-free at 6, 9 and 12-months. These limits remain above 80% when assessed per arm. These lower limits are higher (>0.9) if we use the 6-month timepoint for assessing double-negativity. We will also estimate the sensitivity and specificity of GB for detecting recurrence overall. We are targeting ≥92% sensitivity for all BC recurrences (≥98% for high-grade recurrences). For sensitivity, we would obtain 95% Wilson CIs of approx. 84-96% if sensitivity is 92%, assuming that we have 75 events (assuming c.80% of events detected by cystoscopy have corresponding GB test data available). This corresponds to being able to rule out sensitivity of approximately 80% or lower per arm (based on 38 events). For specificity, GB false-positives will only be considered as genuine false-positives (and not pre-emptive diagnosis) if VAFs fall or become undetectable at subsequent test episodes in the absence of visible tumour by cystoscopy.

We will develop a decision-analytic model to evaluate the cost-effectiveness of using GB compared to cystoscopy for long-term surveillance of NMIBC patients. We will investigate the cost-effectiveness of replacing some cystoscopies with GB and if intervals between surveillance episodes can be extended for double-negative patients. We will include the costs and consequences of disease recurrence; the time horizon will be 10-years. The analyses will follow the recommended methods and 'reference case' recommended by NICE, including: an NHS and Personal Social Services perspective for costing; estimation of QALYs using EQ-5D data and UK value sets, and discounting of costs and QALYs at 3.5% per year.

All samples will be identified via a unique trial ID number, with linked anonymisation. In addition, patients will also be asked to sign consent for transfer of samples for use in future analyses, as yet to be defined, linked to the overall objectives of the TRAIN trial with collaborators in other research groups who may be in the UK or abroad and in either the academic or commercial sector. All such work would maintain patient confidentiality and anonymisation in presentation of data.

Any samples remaining once trial analyses are complete will be stored appropriately for future use, if patient consent allows. Southampton CTU will keep record of the conditions of consent for each patient sample. If a patient does not give consent for their samples to be used outside of the trial or subsequently withdraws consent for their samples to be used, Southampton CTU will inform the relevant central laboratory who will be responsible for destroying the samples and confirming this in writing to Southampton CTU once done.

11 REGULATORY COMPLIANCE

11.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) and a Favourable Research Ethics Committee (REC) Opinion

The radiotherapy procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert.

11.2 DEVIATIONS AND SERIOUS BREACHES

11.2.1Protocol Compliance

A protocol deviation is any noncompliance with the trial protocol, GCP, or Manual of Procedure requirements. Any deviation occurring at sites should be reported to the SCTU and the local R&D Office immediately. As a result of deviations SCTU will advise of and/or undertake any corrective and preventative actions as appropriate. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

11.2.2Serious Breaches

A "serious breach" is a breach which is likely to affect to a significant degree –
- The safety or physical or mental integrity of the participants of the trial; or
- The scientific value of the trial.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

The SCTU will assess serious breaches and advise centers on any corrective and preventative actions. The SCTU will notify the Sponsor, who will assess the breach and determine if it meets the criteria of a 'serious' breach.

12 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the trial, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment or legal rights.

12.1 RESEARCH ETHICS COMMITTEE REVIEW (REC) AND REPORTS

The trial protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

Within one year after the end of trial, the Chief Investigator will submit a final report with the results, including any publication/abstracts, to the REC.

12.2 SPECIFIC ETHICAL CONSIDERATIONS

The SCTU uses the electronic data capture tool called RAVE, which will be used in the TRAIN trial for sites to input anonymised trial data. The servers that this database will be held on are based in the USA and therefore being stored outside of the UK and EEA. The Patient Information Sheet and Consent (PISC) form shall highlight to patients where the data will be held.

12.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the participant information sheet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason without the standard of their care or legal rights being negatively affected. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friends or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

12.4 DATA PROTECTION AND CONFIDENTIALITY

The Southampton Clinical Trials Unit (SCTU) will be the data custodian for this trial. SCTU will preserve the confidentiality of participants taking part in the trial. The investigator must ensure that participants' anonymity will be maintained and that their identities are protected from unauthorised parties. On eCRFs participants will not be identified by their names, but by an identification code.

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 and the UK Policy Framework for Health and Social Care Research with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Patients will be identified by a unique study number. The patient's name and hospital number will not be used. Any information about patients which leaves the hospital will have their name, address, hospital number and other personal identifiable information removed so that their identity remains confidential.

The clinical research team at site will have access to patient medical notes and the clinical investigation results. Delegates of the Sponsor's, i.e., Southampton Clinical Trials Unit will have access to the medical notes for the purposes of monitoring. Regulatory authorities will also have access to the medical notes, if required, if sites are inspected. Patient's consent will be obtained for this at the start of the trial.

Data will be entered onto an electronic data capture system (Medidata Rave) by site staff. It will be analysed by the statisticians at Southampton Clinical Trials Unit.

Any data collected by SCTU as part of the trial will be securely stored in line with the Data Protection Act 2018 and GDPR. Patient trial data and medical records will be stored for a minimum of 25 years in accordance with the Medicine for Human Use (Clinical Trials) Regulations. Data will be stored at site using local storage arrangements. Research data will be stored in a Sponsor approved long term storage facility.

13 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor (The Christie NHS Foundation Trust) and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

13.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

13.2 FUNDING

The National Institute for Health and Care Research (NIHR) are funding this study, with additional support from SCTU core funding.

13.3 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

This study is adopted onto the NIHR portfolio. This enables Trusts to apply to their Local Clinical Research Network for service support costs, if required.

13.4 PARTICIPANT PAYMENTS

Participants will not be paid for participation in this trial.

14 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU, and oversight will be maintained by the Trial Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee.

14.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the trial, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the trial.

The TRAIN TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

14.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The TRAIN TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

14.3 DATA MONITORING AND ETHICS COMMITTEE (DMEC)

The aim of the DMEC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

The TRAIN DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the DMEC, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other trial committees.

15 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared, including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created. Timelines for key tasks will be specified in the DMP and shared with sites during the Site Initiation Visits.

Data queries will either be automatically generated within the eCRF, or manually raised by the trial team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

16 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

17 MONITORING

17.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be raised to the site in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU within the required timeframe. The forms will then be filed along with the appropriate CRFs, and the appropriate corrections made on the database. There are several monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

Consent forms received by SCTU staff will be checked regularly following the TMP and relevant SCTU SOPs.

17.2 CLINICAL SITE MONITORING

Clinical site monitoring frequency will be determined by the recruitment figures at each participating centre as detailed in the TMP. Triggered site monitoring will occur where required.

17.2.1 Source Data Verification

Upon receipt of a request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to trial staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, including representatives of the

Competent Authority. Details will remain confidential and participants' names will not be recorded outside the trial site without informed consent.

17.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

17.4 AUDITS AND INSPECTIONS

The trial may be subject to inspection and audit by The Christie NHS Hospital Trust (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

18 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. Archiving will be authorised by the Sponsor following submission of the end of trial report. All source and trial related documents will be retained for a period of 25 years following the end of the trial. After the completion of the trial, remote monitoring may be carried out using NHS health record systems including NHS digital cancer registries for approved future research.

Sites are responsible for archiving the ISF and participants' medical records. Following the period of retention destruction of essential documents will require authorisation from the Sponsor.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

19 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors, then a 'writing committee' will be identified. All publications will be reviewed by the Sponsor prior to finalising and submitting.

Participants will not be contacted directly with the results of the trial but a link to any publication with findings will be included on the SCTU website and publicised via social media channels.

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21 APPENDICES

21.1 APPENDIX A - COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE V5)

Please go to the following website to access the NCI CTCAE Version 5.0.

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

21.2 APPENDIX B - RTOG MORBIDITY SCORE – RADIATION MORBIDITY OF THE BLADDER AND INTESTINES

	0	1	2	3	4	5
Bladder	No morbidity	Slight epithelial atrophy; minor telangiectasia (microscopic haematuria)	Moderate frequency; generalised telangiectasia; intermittent macroscopic haematuria	Severe frequency and dysuria; severe generalised telangiectasia (often with petechiae); frequent haematuria; reduction in bladder capacity (<150cc)	Necrosis/contracted bladder (capacity <100cc); severe haemorrhagic cystitis	Death due to toxicity
Small/large intestine	No morbidity	Mild diarrhoea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhoea and colic; bowel movement >5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/perforation fistula	Death due to toxicity

21.3 APPENDIX C - WHO ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature—for example, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. 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
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden,
E.T., Carbone, P.P.:Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol5:649-655, 19

22 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
v1 15-Aug-2025	First version of the protocol.
v2 31-Oct-2025	Updated contraception requirements to 6 months from after end of study. Hypersensitivity to the IMP's or any of their excipients and contraindications to the IMP's added as exclusion criteria. Physical exam and vital signs added to trial schedule. References to BCG and nicotinamide SmPC's added to the protocol. Added the following to prohibited concomitant medications: •Any investigational drug (also for indications different to anticancer therapy) •For participants administered 5-Fluorouracil, the following are contraindications with 5-FU and must be prohibited for participants being administered 5-FU: previous treatment with brivudine, sorivudine or their chemically related analogues •Any other medication contraindicated as per SmPC of all IMPs must be listed
v3 23-Jan-2026	Added that screening cystoscopies can be performed within 6 weeks of randomisation. Added TRAIN-Gen translational study information to the protocol.