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# A randomised Phase III trial to assess whether radiotherapy with radiosensitisers is beneficial in patients with high-risk non-muscle invasive bladder cancer when compared with the standard of care treatment, Bacillus Calmette-Guerin

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| **Submission date**<br>11/09/2025 | **Recruitment status**<br>Recruiting | [X] Prospectively registered<br>[ ] Protocol<br>[ ] Statistical analysis plan<br>[ ] Results<br>[ ] Individual participant data<br>[X] Record updated in last year |
| **Registration date**<br>13/10/2025 | **Overall study status**<br>Ongoing | |
| **Last Edited**<br>09/12/2025 | **Condition category**<br>Cancer | |

## Plain English summary of protocol

Background and study aims

In the UK 20,000 people develop urothelial bladder cancer each year with 75-80% having non-muscle invasive bladder cancer (NMIBC). The current standard of care for patients with high-risk NMIBC (HR-NMIBC) is either surgery to remove the tumour (transurethral resection of bladder tumour; TURBT) followed by BCG (Bacillus Calmette Guérin, an immunotherapy drug) given directly into the bladder, or surgery to remove the bladder (cystectomy). BCG is given weekly for 6 weeks followed by maintenance treatment up to 3 years. However, in up to 50% of patients their cancer returns (recurrence) or gets worse (progression) after BCG and 25% stop treatment due to side effects. Globally BCG supply has been restricted in recent years, increasing HR-NMIBC recurrence rates and costs. Improved treatments are required to prevent recurrence, progression and cystectomy and mitigate the effects of unpredictable supply.

Trimodality treatment (TMT) is maximal TURBT + radiotherapy + a radiosensitiser (gemcitabine, mitomycin C/fluorouracil or carbogen/nicotinamide) and is an equivalent alternative treatment to cystectomy for muscle-invasive bladder cancer (MIBC). TMT is not routinely used for HR-NMIBC. A study found that 54% of HR-NMIBC patients who received TMT did not have recurrence within 5 years. Modern radiotherapy is expected to further improve outcomes and minimise side effects. This study will test if radiotherapy with radiosensitisation improves outcomes for people with HR-NMIBC compared to BCG.

Who can participate?

Patients aged over 16 years with HR-NMIBC following maximal TURBT

What does the study involve?

Patients will be randomly allocated to BCG or radiotherapy with radiosensitisation. Patients in

the experimental group will receive 55 Gy in 20 fractions. Investigators can then choose from three different options for the radiosensitiser. All patients will be followed up for a minimum of 2 years to record their response to treatment.

What are the possible benefits and risks of participating?
The main risks are the potential side effects from the radiosensitiser drugs and the radiotherapy. These are outlined in the patient information sheet. Patients will be encouraged to discuss these with the research team and the patient will be monitored regularly to assess any side effects of the treatment.
During the study, additional blood will be collected from a vein, which may cause pain when the needle is inserted. There is a small risk of bruising or infection at the site of insertion. Some people may experience dizziness, an upset stomach or fainting when blood is taken, however, every effort will be made by hospital staff to minimise this.
Patients who are pregnant or breastfeeding will be excluded from the trial, however, there is a risk to pregnancy during the trial. This risk will be minimised through the use of effective contraception until 3 months post end of study.

Where is the study run from?
University of Southampton (UK)

When is the study starting and how long is it expected to run for?
September 2025 to October 2031

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
1. Dr Daniel Griffiths, train@soton.ac.uk
2. Dr Ananya Choudhury, Ananya.choudhury@nhs.net

Plain English summary under review with external organisation

# Contact information

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Scientific

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Principal investigator

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# Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### Integrated Research Application System (IRAS)
1012385

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
CFTsp223

# Study information

### Scientific Title
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

### Acronym
TRAIN

### Study objectives
Primary objective:
To compare event-free survival between BCG and radiotherapy with radiosensitisation

Secondary objectives:
1. To compare each component of the primary outcome between BCG and radiotherapy with radiosensitisation
2. To determine the difference between BCG and radiotherapy with radiosensitisation for patient-reported symptoms
3. To determine the difference in cancer specific survival between groups
4. To establish tolerability and safety of radiotherapy with radiosensitisation
5. To determine the difference in treatment fidelity between the groups
6. To determine the cost-effectiveness of radiotherapy with radiosensitisation compared to BCG

## Ethics approval required
Ethics approval required

## Ethics approval(s)
approved 05/11/2025, North West - Greater Manchester South Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; -; gmsouth.rec@hra.nhs.uk), ref: 25/NW/0295

## Study design
Open randomized controlled parallel-group trial

## Primary study design
Interventional

## Study type(s)
Efficacy, Safety

## Health condition(s) or problem(s) studied
High-risk non-muscle invasive bladder cancer

## Interventions
This trial is an unblinded randomised Phase III trial. Patients will randomly be allocated to one of two trials arms. The first arm (control) is the current standard of care for this patient group which is BCG. BCG is given 6 weekly by intravesical instillations, followed by three weekly instillations at 3, 6, 12, 18, 24, 30, 36 months. The second arm (experimental) arm is radiotherapy with radiosensitiser drugs. Radiotherapy is given 55 Gy in 20 fractions treating once daily Monday to Friday over 4 weeks. Radiosensitiser as one option from the following:
1. Gemcitabine 75: 100mg/m2 via intravenous infusion administered once a week during a 4-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
2. 5-FU and Mitomycin C: Fluorouracil 500 mg/m2 on days 1 to 5 and 16 to 20 via continuous infusion. Mitomycin C 12 mg/m2 on day 1 via intravenous infusion
3. Carbogen and nicotinamide (CON): Carbogen (2% CO2 and 98% O2) 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 40-60 mg/kg will be taken 1.5 to 2 hours before radiotherapy.

## Intervention Type
Drug

## Phase
Phase III

## Drug/device/biological/vaccine name(s)
Gemcitabine, fluorouracil, mitomycin C, 5% carbon dioxide/oxygen medical gas mixture, nicotinamide

## Primary outcome(s)

Event-free survival, 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 3-4 months as per standard of care and in accordance with NICE guidelines to capture progression and recurrence data.

### Key secondary outcome(s))

1. Recurrence-free survival: time from randomisation to recurrence or end of trial
2. Progression-free survival: time from randomisation to progression or end of trial
3. Metastasis-free survival: time from randomisation to metastasis or end of trial
4. Cancer-specific survival: time from randomisation to cancer diagnosis or end of trial
5. Cystectomy-free survival: time from randomisation to cystectomy or end of trial
6. Overall survival: time from randomisation to death or end of trial
7. Treatment fidelity measured using the summary statistics for treatment delays, missed treatment, those not starting treatment, and those who completed treatment, by group at end of treatment
8. Adverse events measured using Common Terminology Criteria for Adverse Events (CTCAE) v5 at 24 weeks
9. Cost-effectiveness measured using Modular Resource-Use Measure (ModRUM) at 96 weeks
10. Late radiation morbidity of the bladder and intestines measured using Radiation Therapy Oncology Group (RTOG) at 96 weeks
11. Patient-reported outcomes:
11.1. Quality of life and the cost-effectiveness measured using EQ-5D at baseline, then 12, 24, 36,48,60, 72, 84 and 96 weeks from initiation of treatment
11.2. Quality of life measured using the International Prostate Symptom Score (IPSS) at baseline, then 12, 24, 36,48,60, 72, 84 and 96 weeks from initiation of treatment then every 6 months until the end of study
11.3. Quality of life measured using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30) at baseline, then 12, 24, 36,48,60, 72, 84 and 96 weeks from initiation of treatment
11.4. Quality of life measured using EORTC-QLQ-NMIBC24 at baseline, then 12, 24, 36,48,60, 72, 84 and 96 weeks from initiation of treatment

### Completion date

31/10/2031

## Eligibility

### Key inclusion criteria

1. Diagnosed with histologically confirmed grade 3 T1N0M0 transitional cell carcinoma, or carcinoma in situ of the bladder (and N0M0), 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 outline 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

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Mixed

### Lower age limit
16 years

### Upper age limit
100 years

### Sex
All

### Total final enrolment
0

### Key exclusion criteria
1. MDT selected patients with HR-NMIBC who are deemed best suited for primary cystectomy (patients that have trained 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 localised 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 breastfeeding
9. Not able to use appropriate adequate effective contraception during and for 3 months after the study

### Date of first enrolment
01/02/2026

### Date of final enrolment
01/12/2028

## Locations

### Countries of recruitment
United Kingdom

England

**Study participating centre**
**The Christie**
550 Wilmslow Road
Withington
Manchester
England
M20 4BX

**Study participating centre**
**Rosemere Cancer Centre**
Sharoe Green Ln
Fulwood
Preston
England
PR2 9HT

**Study participating centre**
**Royal Lancaster Infirmary**
Ashton Road
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LA1 4RR

**Study participating centre**
**Royal Surrey County Hospital**
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GU2 7XX

**Study participating centre**
**Royal Surrey County Hospital**
Egerton Road
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**Study participating centre**
**Diana, Princess of Wales Hospital**
Scartho Road
Grimsby
England
DN33 2BA

**Study participating centre**
**Stepping Hill Hospital**
Stockport NHS Foundation Trust
Stepping Hill Hospital
Poplar Grove
Stockport
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SK2 7JE

**Study participating centre**
**University Hospital Ayr**
Dalmellington Road
Ayr
Scotland
KA6 6DX

**Study participating centre**
**Peterborough City Hospital**
Edith Cavell Campus
Bretton Gate
Bretton
Peterborough
England
PE3 9GZ

**Study participating centre**
**Wycombe Hospital**
Queen Alexandra Road
High Wycombe
England
HP11 2TT

# Sponsor information

**Organisation**
The Christie NHS Foundation Trust

**ROR**
https://ror.org/03v9efr22

# Funder(s)

**Funder type**
Government

**Funder Name**
National Institute for Health and Care Research

**Alternative Name(s)**
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**
Individual participant data will be made available, including data dictionaries, for approved data-sharing requests. Individual participant data will be shared that underlie the results reported in this article, after de-identification and normalisation of information (text, tables, figures, and appendices). The study protocol and statistical analysis plan will also be available. Anonymous data will be available for request from three months after publication of the 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, signed a Data Sharing Agreement. Data will be shared once all parties have signed relevant data-sharing documentation, covering SCTU conditions for sharing and if required, an additional Data Sharing Agreement from Sponsor. Proposals should be directed to ctu@soton.ac.uk.

**IPD sharing plan summary**
Available on request

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |
| Study website | Study website | 11/11/2025 | 11/11/2025 | No | Yes |