# A phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer

Submission date	Recruitment status No longer recruiting	[X] Prospectively registered		
20/01/2020		[X] Protocol		
Registration date	Overall study status	Statistical analysis plan		
27/01/2020	Ongoing	Results		
<b>Last Edited</b> 03/01/2023	<b>Condition category</b> Cancer	Individual participant data		
		Record updated in last year		

# Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-proton-beam-radiotherapy-for-oropharyngeal-cancer-torpedo

# Contact information

# Type(s)

Scientific

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# Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

Integrated Research Application System (IRAS)

268843

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number

CPMS 43839, IRAS 268843

# Study information

#### Scientific Title

A phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer

## Acronym

**TORPEdO** 

# **Study objectives**

The number of cases of cancers arising from the tonsil and back of the tongue is rising worldwide. Even when this type of cancer is large or has spread to lymph nodes in the neck (called locally advanced cancer), it usually responds well to treatment and most people are cured. However, treatment with radiotherapy combined with chemotherapy can cause severe side effects during treatment. In the long term, this has the potential for significant harmful impact on quality of life.

This study includes patients with locally advanced cancers of the tonsil and back of the tongue. It will focus on whether proton beam therapy (a newer form of radiotherapy) can reduce side effects and improve patient-reported quality of life compared with standard radiotherapy (called intensity-modulated radiotherapy). Proton beam therapy can be directed more precisely than standard radiotherapy. This reduces the amount of normal tissue receiving radiation that isn't wanted. It is known from international use of proton beam therapy (e.g. the USA) that it is a safe treatment and is thought to cause less damage to normal tissues.

# Ethics approval required

Old ethics approval format

# Ethics approval(s)

Approved 12/12/2019, North West - Greater Manchester West Research Ethics Committee (Barlow House 3rd Floor, 4 Minshull Street, Manchester M1 3DZ, UK; Tel: +44 (0)207 104 8021; Email: nrescommittee.northwest-gmwest@nhs.net), REC ref: 19/NW/0700

# Study design

Randomised; Interventional; Design type: Treatment, Radiotherapy

# Primary study design

Interventional

# Study type(s)

Treatment

# Health condition(s) or problem(s) studied

Oropharyngeal cancer

#### **Interventions**

Participants will be recruited from selected sites across the UK. Potential participants will be identified by their clinical care teams and their suitability will be discussed at local multidisciplinary team meetings. Participants will have locally advanced oropharyngeal squamous cell carcinoma prostate cancer and have opted to have chemo-radiotherapy as radical treatment.

Participants will be approached by a member of their clinical care team and will receive a verbal explanation of the trial, together with a Patient Information Sheet which they will take home with them. They will be given sufficient time to make a decision about whether they would like to participate and will be able to discuss their options with friends, family or their GP. They will have the opportunity to raise any questions about TORPEdO with their clinical care or research team and these will be addressed prior to their decision about whether to participate. Should they chose to participate they will be asked to sign a consent form to record their informed consent.

All participants will be randomised via the central randomisation service provided by the Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU). Participants will be randomised using a computer-generated minimisation technique which ensures balance between the treatment groups. Using this technique, the treatment allocation for each participant depends on the characteristics of the participants already involved, thus minimising imbalance across any factors that might predict outcome.

The following assessments will be performed prior to randomisation into TORPEdO:

- a) Complete medical history, physical examination (including weight and height), WHO performance status (PS)
- b) Pre-radiotherapy dental assessment (may be conducted at randomising centre or proton centre)
- c) Blood to be taken for full blood count, renal function (calculated GFR/isotope depending on local hospital policy)

electrolytes and liver function tests

- d) Completion of baseline Patient Reported Outcomes (PRO) questionnaires
- e) Swallowing function assessments
- f) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)
- g) Radiological assessment of oropharyngeal cancer: all patients will be clinically assessed and radiologically staged in line with standard practice. Radiological assessment should include as a minimum: MRI neck & CT thorax preferred, however CT neck + CT thorax is acceptable h) Histology report
- i) ECG/BSA (concurrent chemotherapy assessments) considered as per local hospital policy

# TORPEdO pre-treatment assessments (after randomisation):

- a) Dental assessment for patients who did not have this done as part of the screening assessments
- b) NM isotope GFR (depending on local hospital policy as this is not mandated by the trial protocol) for patients who did not have this conducted as part of the screening assessments (however calculated renal function should have been conducted to ensure eligibility for the trial)
- c) Audiometry assessment
- d) Maximum interincisal distance to assess for trismus
- e) Baseline assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0.
- f) DW-MRI (for patients taking part in the optional DW-MRI sub-study at The Christie Hospital)

#### TORPEdO during treatment assessments:

Treatment will be given over 6.5 weeks, patients will be seen at the end of each week and the following assessments will be performed:

- a) Patient weight (to assess any weight loss) and WHO PS
- b) Blood to be taken for full blood count, electrolytes, liver function tests
- c) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)
- d) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0
- e) DW-MRI (for patients taking part in the optional DW-MRI sub-study at The Christie Hospital) during week 3 of treatment

For IMPT patients all on treatment assessments will take place at the Proton centre.

# TORPEdO end of treatment assessments (end of week 7):

- a) Patient weight (to assess any weight loss) and WHO PS
- b) Blood to be taken for full blood count, electrolytes, liver function tests
- c) Completion of PRO questionnaires
- d) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)
- e) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0

# TORPEdO post treatment assessments:

#### At 6 weeks post treatment:

- a) Patient weight (to assess any weight loss) and WHO PS.
- b) Completion of PRO questionnaires.
- c) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use).
- d) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0.
- e) Clinical response assessment.

#### At 3, 6, 12, 18, 24 post treatment:

a) Patient weight (to assess any weight loss) and WHO PS

- b) Completion of PRO questionnaires
- c) Swallowing function assessments
- d) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)
- e) Audiometry assessment (3 months, 12 months, 24 months)
- f) Maximum interincisal distance to assess for trismus (3 months, 12 months, 24 months)
- g) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0 and LENT SOMA
- h) All patients will undergo clinical and radiological assessment to determine their response to treatment 12-14 weeks after completion of radiotherapy. Radiological assessment will be in line with standard practice: PET-CT is preferred, however MRI neck + CT Thorax acceptable. Imaging may be performed earlier if clinically indicated, e.g. if there is a clinical suspicion of residual disease
- i) Clinical response assessment at 6, 12, 18 and 24 months to determine disease response. Further radiological review should be carried out as per standard practice if clinical assessment raises the suspicion of recurrent disease
- j) Healthcare resource-use (3, 6, 12 months).

# At 3, 4, 5 years post treatment:

- a) Completion of PRO questionnaires
- b) Assessment for recurrence and survival only

#### Annual visits after 60 months:

Patients will not be required to undergo any trial-specific investigations, however, data will be requested annually from standard follow visits relating to patients disease status, survival and health resource usage assessment.

# Patient-reported outcomes

TORPEdO participants will take part in the QL study. They will be asked to complete a patient-reported outcomes questionnaire before radiotherapy, at the end of radiotherapy (week 7) and at week 6. Further questionnaires will be at 3, 6, 12, 18, 24, 36, 48 and 60 months. The initial questionnaires will be handed to patients at clinic visits and those from 3 months onwards will be posted directly to patients' homes. The questionnaires should take no more than 30 minutes to complete.

# Translational sub-studies (optional)

Patients will be asked to gift archival tumour tissue and blood samples as part of optional substudies. Blood sampling will coincide with collection of routine clinical bloods (no separate needle sticks):

EDTA blood (10 ml) for genomics (taken at 1 timepoint)

Streck bloods (40 ml on first occasion; 30 ml thereafter) for liquid biopsies (taken at 4 timepoints)

EDTA bloods (30 ml) for immune markers (taken at 4 timepoints).

EDTA bloods (10 ml) for proteomics (taken at 10 timepoints)

MRI substudy (for The Christie patients only - optional)

One MRI scan before treatment starts and a second MRI scan during the third week of treatment.

# Quality assurance, training and patient safety

Detailed technical radiotherapy planning and delivery guidelines will be in place for TORPEdO. These will set out exactly how the radiotherapy should be given. They will include details of the safety margins to be added around the treatment area, mandatory limits relating to the proportion of the total radiotherapy dose to which normal tissue can be exposed (dose constraints) and how participants should be prepared to receive treatment.

In addition to the technical radiotherapy guidelines, a comprehensive quality assurance programme led by the National Clinical Research Institute Radiotherapy Clinical Trials Quality Assurance (NCRI RTTQA) group will be put in place to ensure quality and consistency of radiotherapy delivery to participants within and between TORPEdO centres. Centres will have to pass components of this programme before they are approved to recruit TORPEdO participants. TORPEdO trial teams at participating sites will also receive training from the TORPEdO trial manager on the trial protocol and logistics at a site initiation meeting prior to commencing recruitment. Only when a centre has satisfactorily completed the pre-trial quality assurance and training, will they be able to invite patients to participate in TORPEdO. Quality assurance processes will be ongoing throughout TORPEdO.

Patient safety will be monitored by the Independent Data Monitoring Committee (IDMC) who will review all safety and efficacy data by treatment group.

Central trial management will be conducted by the ICR-CTSU, a UKCRC registered NCRI cancer clinical trials unit.

Participants will be recruited to TORPEdO at participating sites for approximately 33 months. Where possible, follow up data will continue to be collected for all trial participants from routine clinic visits until their death, to contribute to the planned secondary endpoint analyses which will be published as data becomes available. Analysis of all primary and secondary endpoints will be conducted by ICR-CTSU. A Trial Management Group (TMG) will be set up and will have responsibility for day to day management of the trial. It will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups membership will include a lay/consumer representative.

The independent Trial Steering Committee (TSC) will meet annually throughout TORPEdO to oversee the study's progress on behalf of the sponsor and funder. The IDMC will meet in confidence, at least annually, to review the data and make recommendations as appropriate to the TSC and TMG.

# Intervention Type

Other

#### **Phase**

Phase III

# Primary outcome(s)

Co-primary endpoints:

- 1. University of Washington Quality of Life Questionnaire (UW-QoL) physical composite score
- 2. Gastrostomy dependence or CTCAE grade 3 weight loss (i.e. ≥ 20% weight loss from baseline) Timepoint(s): 12 months after completion of chemoradiotherapy

#### Key secondary outcome(s))

- 1. Health-related quality of life (HR-QoL) evaluated using the PRO questionnaires at baseline, end of treatment, 6 weeks post-treatment and at 3, 6, 12, 18, 24, 36, 48, and 60 months post-treatment
- 1.1. University of Washington Quality of Life (UW-QoL)
- 1.2. EORTC OLO-C30 and OLO-H&N43

- 1.3. M.D. Anderson Dysphagia Inventory (MDADI)
- 2. Tube feeding status evaluated at 3, 12, 18 and 24 months after completion of treatment
- 3. Acute and late severe toxicity assessed by physician recorded CTCAE v 5.0 and physician-rated dysphagia scores at baseline, week 1, week 2, week 3, week 4, week 5, week 6 (during treatment) week 7 (end of treatment), 3, 6, 12, 18 and 24 months post-treatment
- 4. Swallowing function evaluated using the 100-mL Water Swallowing Test at baseline, and at 3, 6, 12, 18 and 24 months following completion of study treatment
- 5. Performance Status Scale for Head and Neck Cancer (PSS-HN) Normalcy of Diet and Place of Eating scores reported at baseline, and at 3, 6, 12, 18 and 24 months following completion of study treatment
- 6. Hearing measured by audiometry at baseline, and at 3, 12 and 24 months post-treatment
- 7. Trismus evaluated using change in maximum interincisal distance at baseline, and at 3, 12 and 24 months post-treatment
- 8. Resection rate, defined as the proportion of patients proceeding to surgical treatment (including neck dissection) after the completion of radiotherapy treatment
- 9. Loco-regional tumour control, defined as time from randomisation to loco-regional recurrence i.e. recurrence at the primary site or in the neck
- 10. Overall survival, defined as time from randomisation to death from any cause
- 11. Cost-effectiveness analysed using the healthcare resource use questionnaire developed for the trial, Work Productivity Assessment Index (WPAI-SHP) and EuroQol five-dimensional questionnaire (EQ-5D-5L) at baseline, end of treatment, 6 weeks post-treatment and at 3, 6, 12, 18, 24, 36, 48, and 60 months post-treatment

# Completion date

01/09/2028

# Eligibility

## Key inclusion criteria

- 1. Histologically confirmed oropharyngeal squamous cell carcinoma
- 2. HPV positive TNM8: T1-2 N1-2 (excluding T1-2 with a single ipsilateral node < 3cm), T3-4 N0-2
- 3. HPV negative TNM 8: T1N2, T2N1-N2, T3-4N0-2
- 4. Local MDT decision for concurrent chemoradiotherapy with bilateral neck treatment
- 5. Age > = 18 years
- 6. WHO performance status 0-1
- 7. Adequate renal function, glomerular filtration rate (GFR) > 60ml/min calculated using Cockcroft-Gault formula
- 8. Adequate cognitive ability (in the opinion of the local PI) to complete PRO assessments
- 9. Willingness to comply with the protocol, including travel to the proton centre for IMPT treatment
- 10. Written informed consent

# Participant type(s)

Patient

# Healthy volunteers allowed

No

#### Age group

Adult

# Lower age limit

18 years

#### Sex

All

# Key exclusion criteria

- 1. Feeding tube insertion required for nutrition due to dysphagia prior to treatment [Note: patients who have prophylactic feeding tube insertion, with or without tube use to top up nutrition prior to starting treatment, remain eligible for the study]
- 2. N3 disease
- 3. Upfront neck dissection
- 4. Use of induction chemotherapy
- 5. Previous head and neck radiotherapy
- 6. Major surgery within 6 months of trial entry
- 7. Permanent pacemaker or implantable cardioverter-defibrillator
- 8. Any invasive malignancy within previous 2 years (other than non-melanomatous skin carcinoma or cervical carcinoma in situ)
- 9. Previous or concurrent illness (e.g., active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis), which in the investigator's opinion would interfere with completion of therapy, trial assessments or follow up 10. Pregnancy; lactating women or women of childbearing potential unwilling or unable to use adequate non-hormonal contraception (male patients should also use contraception if sexually active)
- 11. Pre-existing speech or swallowing problems unrelated to the diagnosis of cancer

For patients taking part in the optional DW-MRI study at The Christie Hospital the following additional exclusion criteria apply:

- 1. Any contraindication to MRI scanning, including metallic heart valve replacement, permanent pacemaker, implantable cardiac defibrillator, non-MRI compatible metal implants, neuro-stimulators
- 2. A history of allergy/reaction to Gadolinium contrast

#### Date of first enrolment

15/02/2020

#### Date of final enrolment

01/09/2023

# Locations

#### Countries of recruitment

United Kingdom

England

Wales

#### The Christie NHS Foundation Trust

550 Wilmslow Road Withington Manchester United Kingdom M20 4BX

# Study participating centre Leeds Teaching Hospitals NHS Trust

St. James's University Hospital Beckett Street Leeds United Kingdom LS9 7TF

# Study participating centre

The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Freeman Hospital
Freeman Road
High Heaton
Newcastle-upon-Tyne
United Kingdom
NE7 7DN

# Study participating centre Sheffield Teaching Hospitals NHS Foundation Trust

Northern General Hospital Herries Road Sheffield United Kingdom S5 7AU

# Study participating centre University Hospitals Bristol NHS Foundation Trust

Marlborough Street Bristol United Kingdom BS1 3NU

# Study participating centre

# Royal United Hospitals Bath NHS Foundation Trust

Combe Park Bath United Kingdom BA1 3NG

# Study participating centre University College London Hospitals NHS Foundation Trust

250 Euston Road London United Kingdom NW1 2PG

# Study participating centre

University Hospitals Coventry and Warwickshire NHS Trust

Walsgrave General Hospital Clifford Bridge Road Coventry United Kingdom CV2 2DX

# Study participating centre Portsmouth Hospitals NHS Trust

De La Court House Queen Alexandra Hospital Southwick Hill Road Portsmouth United Kingdom PO6 3LY

# Study participating centre The Royal Marsden NHS Foundation Trust

Fulham Road London United Kingdom SW3 6JJ

# Study participating centre Worcestershire Acute Hospitals NHS Trust

Worcestershire Royal Hospital Charles Hastings Way Worcester United Kingdom WR5 1DD

# Study participating centre University Hospital Southampton NHS Foundation Trust

Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

# Study participating centre Abertawe Bro Morgannwg University LHB

One Talbot Gateway Seaway Drive Seaway Parade Industrial Estate Baglan Port Talbot United Kingdom SA12 7BR

# Study participating centre Torbay and South Devon NHS Foundation Trust

Hengrave House Torbay Hospital Newton Road Torquay United Kingdom TQ2 7AA

# Study participating centre Velindre NHS Trust

Unit 2 Charnwood Court Heol Billingsley Cardiff United Kingdom CF15 7QZ

# Study participating centre University Hospitals Birmingham NHS Foundation Trust

Trust HQ, PO Box 9551 Queen Elizabeth Medical Centre Edgbaston Birmingham United Kingdom B15 2TH

# Study participating centre Nottingham University Hospitals NHS Trust

Trust Headquarters Queens Medical Centre Derby Road Nottingham United Kingdom NG7 2UH

# Study participating centre York Teaching Hospital NHS Foundation Trust

York Hospital Wigginton Road York United Kingdom YO31 8HE

# Sponsor information

# Organisation

Institute of Cancer Research

#### **ROR**

https://ror.org/00dpztj76

# Funder(s)

# Funder type

Charity

#### **Funder Name**

Cancer Research UK; Grant Codes: C58459/A27172

## Alternative Name(s)

CR\_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

# **Funding Body Type**

Private sector organisation

# **Funding Body Subtype**

Other non-profit organizations

#### Location

United Kingdom

#### **Funder Name**

National Institute for Health Research (NIHR) (UK)

## 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

The datasets generated during and/or analysed during the current study are/will be available upon request from (TORPEdO Trial Manager, TORPEdO-icrctsu@icr.ac.uk). Formal responsibility for all data collected within this trial lies with the trial sponsor (ICR). ICRCTSU's Data and Sample Access Policy, available on external-facing web pages, details eligibility criteria for access and how access to collections will be prioritised. Priority will be given to projects from within the original trial proposal and access will usually be reserved for trial purposes until those studies are concluded. Data will not be released where this could impact on the reporting of the primary research questions of the trial.

The policy defines the application process. In the first instance, applicants are encouraged to approach ICRCTSU and/or the Chief Investigator (CI) informally to discuss the feasibility of the proposal including the suitability of the collection for the proposed research. Once feasibility has been established, formal applications are made using the ICRCTSU Sample and Data Access Request Form. Applications should include a clear statement of the study hypothesis, objectives and proposed methodology and details of the responsible person or persons who will carry out

the work. A statistical analysis plan and a power calculation are also required. A preliminary review of complete applications is performed by the CI and ICRCTSU Scientific Lead to ensure that the proposal is achievable and is scientifically sound. If both agree, the application is forwarded to the TMG for review and prioritisation. Once an application has been agreed in principle by the TMG it is submitted to the TSC for final approval. If approved, the applicant must agree to the conditions of access in writing under an access agreement between the applicant's host institution and the sponsor. Identifying data is not made available to applicants. Data must be stored in a secure location with access strictly controlled and overseen by those named on the application. Applicants are asked to provide a lay summary of their research project, as well as an end of project report or publication of the results to the TMG.

# IPD sharing plan summary

Available on request

# **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		21/11/2022	29/12/2022	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	v4.0	28/04/2021	29/12/2022	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol (other)	v5	09/02/2022	29/12/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes