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A feasibility trial to test whether having all treatment before surgery is a better way of treating oesophageal cancer

Submission date 07/03/2026	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 01/06/2026	**Overall study status** Ongoing	
Last Edited 01/06/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Oesophageal adenocarcinoma (OAC) is a type of cancer found in the food pipe (oesophagus). Despite improvements in treatments, more than half of people diagnosed with OAC don't survive more than 5 years after diagnosis (although this improves when diagnosed early and if the patient is younger and fit). Currently, if OAC is thought to be 'potentially curative' at diagnosis, patients will undergo chemotherapy (termed FLOT) or chemoradiotherapy (a mixture of chemo- and radiotherapy, termed CROSS) to shrink the tumour before it is surgically removed. With FLOT, patients undergo four cycles of chemotherapy before surgery and four more cycles after. Patients undergoing CROSS receive a mixture of chemotherapy with radiotherapy before surgery and sometimes immunotherapy to help the immune system to fight any remaining cancer.
Completing either of these provides the best chance at living cancer-free after surgery; however, this can be challenging, and less than half of people undergoing chemotherapy after surgery complete all four cycles.
Pressures during the COVID-19 pandemic meant that some people with OAC had all their chemotherapy before surgery (termed total neoadjuvant treatment or TNT), and many of these individuals are living cancer-free more than 5 years on. We want to find out if this method of delivering FLOT (FLOT-TNT) or some FLOT (four cycles) with CROSS (FLOT-CROSS) offers patients with OAC a better chance of completing treatment compared with current FLOT regimens.

Who can participate?
Patients aged 18 to 85 years with newly diagnosed ‘potentially curable’ OAC

What does the study involve?
Participants are randomly (by chance) allocated to one of the three treatments (FLOT-TNT, FLOT-CROSS or standard FLOT). We will compare how well they tolerate their treatment and how they progress through surgery and beyond.

What are the possible benefits and risks of participating?
The results of this study will help us determine whether a larger trial should be carried out to see which of these treatment options should become standard of care for OAC.
Participation in this trial may include some risks and burdens. These have been carefully considered, and processes have been developed to minimise these and their impact on participants and carers.
Several clinical interventions occurring in this trial and as standard of care carry a risk of discomfort and pain. These procedures include blood sampling, insertion of indwelling lines and endoscopic procedures to investigate and biopsy tumours. To minimise the risk of this pain and discomfort, blood will be collected from a prominent and accessible vein where possible by a competent, trained health professional. Indwelling (PICC) lines will be fitted by trained chemotherapy nurses under local anaesthesia. Endoscopy procedures will be performed under mild sedation to minimise discomfort associated with advancing the endoscope and collecting the tumour biopsy.
Standard care and participation in the trial also carry the risk of inconvenience and change to lifestyle due to regular hospital appointments and wearing of the portable IV chemotherapy pump. These inconveniences are common with chemotherapy treatments for cancers and have been introduced to enable participants the freedom to undergo the majority of their chemotherapy delivery time in the comfort of their own homes instead of within a chemotherapy unit or hospital. However, wearing an infusion pump can be inconvenient, cause discomfort and limit the ability to perform certain activities. These will be discussed with your care team to try and minimise the burden of wearing the pump.
Chemo- and radiotherapy are commonly associated with a wide array of side effects which can be limiting and, sometimes, painful. These can also cause nausea, affect your appetite and cause fatigue. Supportive medicines will be provided to try and minimise these effects, and advice will be provided by your care team and via Macmillan support pamphlets with information on how to manage these side effects. There is potentially a greater risk of experiencing side-effects of treatments in the two TNT study arms (FLOT-TNT and CROSS) due to the prolonged period of chemotherapy and/or radiotherapy. These should always be discussed with your care team, and you can stop treatment with the support of your doctor if they become overwhelming.
Information relating to risks and burdens of chemo- and radiotherapy is outlined in the Patient Information Sheet and should be discussed with your doctor or a member of the care team.
The trial sponsor will implement a monitoring team which will respond to identified risks throughout the trial and notify the research team so that the research is modified accordingly.

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

When is the study starting and how long is it expected to run for?
March 2026 to March 2028

Who is funding the study?
Chief Scientist Office (UK)

Who is the main contact?
1. Patricia Burns, TASCgovernance@dundee.ac.uk
2. Prof. Russell Petty, r.petty@dundee.ac.uk

Plain English summary under review with external organisation

Contact information

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Scientific, Public

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Additional identifiers

Integrated Research Application System (IRAS)
1012559

Study information

Scientific Title
Multi-centre, three-arm Phase II/III feasibility, randomised control trial to compare total neoadjuvant treatment to standard of care perioperative chemotherapy in patients with newly diagnosed oesophageal adenocarcinoma eligible for surgery

Acronym
TNT-OAC

Study objectives
Primary objective:
To determine the feasibility of a larger trial to test whether delivering all treatment for oesophageal adenocarcinoma before surgery results in better outcomes compared to the current standard practice of delivering treatment before and after surgery.

Secondary objectives:
1. To compare the tolerability of receiving all treatment before surgery compared to current practice
2. To investigate toxicity relating to receiving all treatment prior to surgery compared to current practice
3. To investigate pathological response following all treatment prior to surgery compared to current practice
4. To investigate surgical outcomes following all treatment prior to surgery compared to current practice
5. To investigate patient-reported quality of life in people who are undergoing and have received all treatment prior to surgery compared with current practice
6. To investigate disease-free survival following all treatment prior to surgery compared to current practice
7. To investigate cancer recurrence following all treatment prior to surgery compared to current practice
8. To investigate overall survival following all treatment prior to surgery compared to current practice

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 13/05/2026, Wales REC 5 (Health and Care Research Wales Floor 4, Crown Building Cathays Park, Cardiff, CF10 3NQ, United Kingdom; -; Wales.REC5@wales.nhs.uk), ref: 26/WA/0082

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Open (masking not used)

Control
Active

Assignment
Single

Purpose
Treatment

Study type(s)

Health condition(s) or problem(s) studied
Oesophageal adenocarcinoma

Interventions

Eligible participants who have provided informed consent will be randomised to one of three study arms (2:2:1 [Arm A: B: C (control)] using minimisation stratified by disease stage [TNM] and disease site) using the online randomisation platform, Sealed Envelope™.

All interventional medicines will be delivered intravenously using standard practice doses in the three study arms as follows:

Arm A (FLOT TNT):
Participants will undergo eight fortnightly cycles of neoadjuvant (before surgery) FLOT chemotherapy before surgical removal of their tumour.

Arm B (FLOT-CROSS TNT):
Participants will undergo four fortnightly cycles of neoadjuvant FLOT chemotherapy followed by five cycles of CROSS chemoradiotherapy (five weekly cycles of carboplatin/paclitaxel combination chemotherapy plus 23 fractions of 1.8 Gy intensity-modulated radiation therapy [IMRT]/volumetric modulated arc therapy [VMAT] radiotherapy) before the surgical removal of their tumour. Participants identified as high risk of cancer spread or recurrence may undergo nivolumab immunotherapy for up to 40 weeks if recommended by their treating physician.

Arm C (FLOT-SoC):
Participants will undergo perioperative FLOT chemotherapy according to current standard of care practice for oesophageal adenocarcinoma (four fortnightly neoadjuvant cycles of FLOT followed by surgical tumour removal and a further four fortnightly adjuvant cycles of FLOT).

All three study groups will be followed up for surgical outcomes at 30 and 90 days after surgery and 30 days after the last treatment (participants from Arm C and Arm B [if undergoing adjuvant nivolumab treatment]).

Participants will be asked to complete validated questionnaires to measure the impact of treatment on their quality of life throughout the treatment duration until 2 years after randomisation (data collected at the first cycle of FLOT, after four cycles of FLOT, at the end of neoadjuvant treatment, 30 days after the last treatment (or 30 days after surgery, whichever occurs first) and 24 months after randomisation).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Carboplatin, paclitaxel, fluorouracil, sodiofolin, oxaliplatin, docetaxel, nivolumab

Primary outcome(s)
The feasibility of total neoadjuvant treatment for oesophageal adenocarcinoma compared to standard perioperative chemotherapy measured from Day 0 (randomisation) to the day of surgery. The primary endpoint is a binary endpoint called “treatment completion” and is either “yes” or “no”. It is defined differently in Arm A and Arm B.
In Arm A patients need to complete six cycles of FLOT and have surgery.
In Arm B, patients need to complete four cycles of FLOT and 90% of CROSS RT fractions and have surgery.

Key secondary outcome(s)

Tolerability of TNT in comparison to standard care, measured using the following from day 0 to week 26:
1. Number of completed FLOT cycles
2. Dose of FLOT components administered
3. Number of CROSS chemotherapy cycles administered
4. Dose of CROSS chemotherapy components administered
5. Number of CROSS RT fractions completed
6. Completion of four cycles of neoadjuvant FLOT in Arms B & C
7. Completion of eight cycles of neoadjuvant FLOT in Arm A
8. Completion of five cycles of neoadjuvant CROSS in Arm B
9. Commencement of postoperative FLOT in Arm C
10. Completion of four cycles of postoperative FLOT in Arm C

Toxicity of TNT in comparison to standard care, measured using the following from day 0 to week 26:
1. Number of adverse events
2. Grade severity of AEs according to CTCAE v6.0

Pathological response of TNT in comparison to standard care, measured using the following at weeks 30-38:
1. Histopathological response according to Mandard criteria
2. Complete histopathological response rate
3. ypT status
4. ypN status (and number of LNs examined)
5. R0 status

Surgical outcomes following TNT in comparison to standard care, measured using the following from day of surgery to 90 days postoperative:
1. Clavien-Dindo Grade 2 or higher surgical complication (including anastomotic leak, pneumonia, respiratory failure, cardiac ischaemia/arrhythmia, thrombus, intra-abdominal sepsis/collection, chyle leak)
2. Unplanned return to theatre
3. Unplanned admission to critical care
4. Unplanned hospital re-admission 30- and 90-day surgical mortality rate
5. Duration of hospital admission after surgery
6. Death (day of surgery to 30 and 90 days postoperative)

Quality of life following TNT in comparison to standard care measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire scores (EORTC QLQ) -C30, EORTC QLQ-OG25, EORTC QLQ-OES18 at the following timepoints:
Week 0 (pre-treatment initiation, first cycle of FLOT)
Week 10/end of fourth cycle of FLOT (all arms)
Week 20/end of neoadjuvant treatment (arms A&B)
Week 22-26 90 days post-surgery (arm C)
Week 34-40/90 days post-surgery (arms A & B)
Week 34-38 (end of adjuvant treatment [arm C])
24 months post-randomisation

Disease-free survival following TNT in comparison to standard care: alive and OAC-free in patients with R0 or R1 resection, progression confirmed by endoscopy and/or CT at months 3-24 post-randomisation

Cancer recurrence following TNT in comparison to standard care: sites of recurrence: local, regional or distant (confirmed by endoscopy and/or CT) at months 3-24 post-randomisation

Overall survival in comparison to standard of care: alive at months 3-24 post-randomisation

Completion date
31/03/2028

Eligibility

Key inclusion criteria
1. Age ≥18 to <85 years
2. Adenocarcinoma of the oesophagus or oesophageal junction, Siewert classification types I and II
3. Suitable for multi-modal (curative) therapy including potentially FLOT and CROSS regimens, according to the local multidisciplinary team
4. Tumour stage ≥T2, any N and M0
5. Level of functioning, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
6. Adequate bone marrow function (WBC ≥3 x 10^9/l; Neutrophil count ≥1.65 x 10^9/l; Hb ≥9 g/dl; platelets ≥ 100 x 10^9/l)
7. Adequate renal function (GFR ≥60 ml/min)
8. Adequate liver function (total bilirubin <1.5 x upper level of normal (ULN); AST <2.5 x ULN; ALT <3 x ULN)
9. Participants with a cardiac history should have a cardiology review and should have a left ventricular ejection fraction >50% (as determined by echocardiography)
10. Adequate respiratory function: participants with symptomatic lung disease should have a pulmonary function test with FEV1.0>65% predicted.

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
85 Years

Sex
All

Total final enrolment
0

Key exclusion criteria

1. Squamous, adenosquamous or other non-adenocarcinoma tumour histology
2. Advanced inoperable or metastatic oesophageal adenocarcinoma
3. Oesophageal adenocarcinoma T1N0 and T4b
4. Oesophageal adenocarcinoma T4a evaluated as not curatively resectable by the local MDT
5. Gastric carcinoma (according to UICC TNM732)
6. Prior chemotherapy for gastrointestinal cancer
7. Clinically significant (active) cardiac disease (e.g. symptomatic coronary artery disease or myocardial infarction within last 12 months)
8. Clinically significant lung disease in the opinion of the investigator
9. Uncontrolled, in the opinion of the investigator, intercurrent physical or mental illness
10. Existing peripheral neuropathy greater than grade 1
11. Concurrent or within 5 years other primary malignancy, except cutaneous squamous cell carcinoma, basal cell carcinoma or cervical carcinoma in situ
12. Prior thorax or intraabdominal radiotherapy
13. Participation in another intervention trial with interference of chemotherapeutic or chemoradiotherapheutic intervention during the last 30 days prior to informed consent
14. Known allergy or hypersensitivity to any of the trial drugs including Dihydropyrimidine dehydrogenase (DPD) deficiency
15. Pregnant or breastfeeding participants, or those who are planning pregnancy

Date of first enrolment
29/06/2026

Date of final enrolment
03/11/2027

Locations

Countries of recruitment
England

Scotland

Wales

Study participating centre
Ninewells Hospital
Ninewells Avenue
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DD1 9SY

Sponsor information

Organisation
University of Dundee

ROR
https://ror.org/03h2bxq36

Funder(s)

Funder type

Funder Name
Chief Scientist Office

Alternative Name(s)
CSO

Funding Body Type
Government organisation

Funding Body Subtype
Local 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 the chief investigator (Prof. Russell Petty, r.petty@dundee.ac.uk). Approval of requests will be at the discretion of the chief investigator. Data will be available after the primary publication of the trial results; there is no end date for requests. Data will be transferred using an appropriate secure method (e.g., encrypted email, file transfer system, or similar) and will be limited to only data required to perform the proposed analysis. Data will be anonymised or pseudonymised as appropriate. Patient consent for data sharing will be obtained at trial entry. The full details and terms of the transfer will be set out in a data sharing agreement.

IPD sharing plan summary
Available on request