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STUDY PROTOCOLS

Personalizing neoadjuvant chemotherapy for locally advanced colon cancer: protocols for the international phase III FOxTROT2 and FOxTROT3 randomized controlled trials

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Abstract

Aim: FOxTROT1 established a new standard of care for managing locally advanced colon cancer (CC) with neoadjuvant chemotherapy (NAC). Six weeks of neoadjuvant oxaliplatin and fluoropyrimidine (OxFp) chemotherapy was associated with greater 2-year disease-free survival (DFS) when compared with proceeding straight to surgery (STS). There is now a need to refine the use of NAC and identify those most likely to benefit. FOxTROT2 will aim to investigate NAC in older adults and those with frailty. FOxTROT3 will aim to assess whether intensified triplet NAC provides additional benefits over OxFp.

Method: FOxTROT2 and FOxTROT3 are international, open-label, phase III randomized controlled trials. Eligible patients will be identified by the multidisciplinary team. Patient age, frailty and comorbidities will be considered to guide trial entry. Participants will be randomized 2:1 to the intervention or control arm: 6 weeks of dose-adapted neoadjuvant OxFp versus STS in FOxTROT2 and 6 weeks of neoadjuvant modified oxaliplatin, 5-fluorouracil and irinotecan versus OxFp in FOxTROT3. The primary endpoint in FOxTROT2 is 3-year DFS. In FOxTROT3, tumour regression grade and 3-year DFS are co-primary endpoints.

Discussion: FOxTROT2 and FOxTROT3 will establish the FOxTROT platform, a key part of our long-term strategy to develop neoadjuvant treatments for CC. FOxTROT2 will investigate NAC in a population under-represented in FOxTROT1 and wider research. FOxTROT3 will assess whether it is possible to induce greater early tumour responses and whether this translates to superior long-term outcomes. Looking ahead, the FOxTROT platform will facilitate further trial comparisons and extensive translational research to optimize the use of NAC in CC.

KEYWORDS
chemotherapy, colon cancer, foxtrot, neoadjuvant, personalising

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INTRODUCTION

Locally advanced colon cancer (CC) has traditionally been managed with surgical resection followed by adjuvant chemotherapy (AC) in those at high risk of recurrence [1]. While this approach is often associated with long-term survival, approximately 40% of patients relapse within 5 years [2]. Hence, developing novel and more effective treatment strategies for treating CC is an area of clinical priority.

The recently published FOxTROT1 trial was the first large phase III randomized-controlled trial (RCT) to illustrate the clinical benefit of delivering neoadjuvant chemotherapy (NAC) prior to surgical resection in patients with locally advanced CC [3]. Here, 6 weeks of oxaliplatin and fluoropyrimidine [5-fluorouracil (5FU) or capecitabine] chemotherapy, followed by surgery and AC was associated with a significant reduction in the number of patients experiencing recurrent or residual disease at 2 years, compared with the standard sequence of upfront surgery followed by AC (16.8% vs. 21.2%, risk ratio = 0.74, $p = 0.042$). Furthermore, NAC was also associated with a reduction in perioperative morbidity and improvements in important secondary outcomes: tumour downstaging, rate of complete (R0) resection and CC-specific survival. FOxTROT1 also highlighted the importance of molecular stratification, as patients with mismatch repair (MMR) deficient (dMMR) CC did not benefit from the use of NAC. Importantly, FOxTROT1 also added to the growing body of evidence establishing tumour regression grade (TRG) as an effective surrogate endpoint for long-term survival outcomes [4], with a strong correlation between greater tumour regression at the time of surgery and 2-year disease-free survival (DFS).

While the overall benefits of using NAC in locally advanced CC were illustrated in FOxTROT1, there is a need to undertake further research to refine its use in clinical practice and cure more patients. In this article, we present the protocols for the FOxTROT2 and FOxTROT3 trials. Older adults and those with frailty were poorly represented in FOxTROT1; only 28% of participants were over 70 years of age (and were required to be of good performance status), whereas approximately half of all new CC diagnoses are made in this age group [2]. FOxTROT2 will therefore investigate the role of NAC in older patients and those with frailty. Conversely, FOxTROT3 will assess whether intensified chemotherapy using modified FOLFOXIRI (mFOLFOXIRI; comprising 5FU, oxaliplatin and irinotecan) provides additional clinical benefit in patients who are fit enough to tolerate triplet chemotherapy (Figure 1).

Together, these trials will establish the FOxTROT platform, a long-term initiative designed to facilitate clinical trials and exploratory research related to neoadjuvant treatment in CC.

METHOD

The protocols for FOxTROT2 and FOxTROT3 are reported in accordance with guidance from the SPIRIT statement [5].

What does this paper add to the literature?

The recently published FOxTROT1 trial established neoadjuvant chemotherapy (NAC) as a new standard treatment option in locally advanced colon cancer. FOxTROT2 will assess the benefit of NAC in older patients and those with frailty. FOxTROT3 will examine the utility of intensified NAC using modified oxaliplatin, 5-fluorouracil and irinotecan. Their rationales and protocols are presented here.

Trial design and setting

FOxTROT2 and FOxTROT3 are international, multicentre, open-label, phase III RCTs that will recruit participants from approximately 50 sites in the UK and further sites worldwide. Local ethical approval will be obtained in each jurisdiction prior to the commencement of study activities. Each site must provide a full treatment pathway, including radiological assessment, provision of surgery and chemotherapy, pathological assessment and clinical follow-up. In addition to a principal investigator, we recommend that each centre identifies designated FOxTROT leads for surgery, oncology, radiology and pathology. Radiology and pathology leads must undertake FOxTROT-specific training before taking on these roles. Participating centres are listed on the ISRCTN registry.

Aims and hypotheses

The overall aim of the FOxTROT platform is to refine and personalize the use of the NAC pathway in locally advanced but resectable CC. FOxTROT2 specifically aims to determine the efficacy of NAC compared with proceeding straight to surgery (STS) for patients who are unsuitable for mFOLFOXIRI due to age, frailty or comorbidities. On the other hand, FOxTROT3 aims to compare the efficacy of intensified mFOLFOXIRI with oxaliplatin and fluoropyrimidine (OxFp) NAC in those who are not limited by age, frailty or comorbidities.

In FOxTROT2, the alternative hypothesis is that the proportion of patients alive and disease-free at 3 years postrandomization is higher in those who received NAC than those going STS. The null hypothesis is that there is no difference in the proportion of patients alive and disease free at 3 years postrandomization between the groups.

FOxTROT3 utilizes TRG and 3-year DFS as hierarchical co-primary endpoints, where DFS is only evaluated as a primary endpoint if TRG provides a significant result. For TRG, the alternative hypothesis is that the distribution of TRG at the time of surgery is superior in those who received mFOLFOXIRI to those who received OxFp. The null hypothesis is that there is no difference in distribution of TRG between the groups. For 3-year DFS, the alternative hypothesis is that the proportion of patients alive and disease free at

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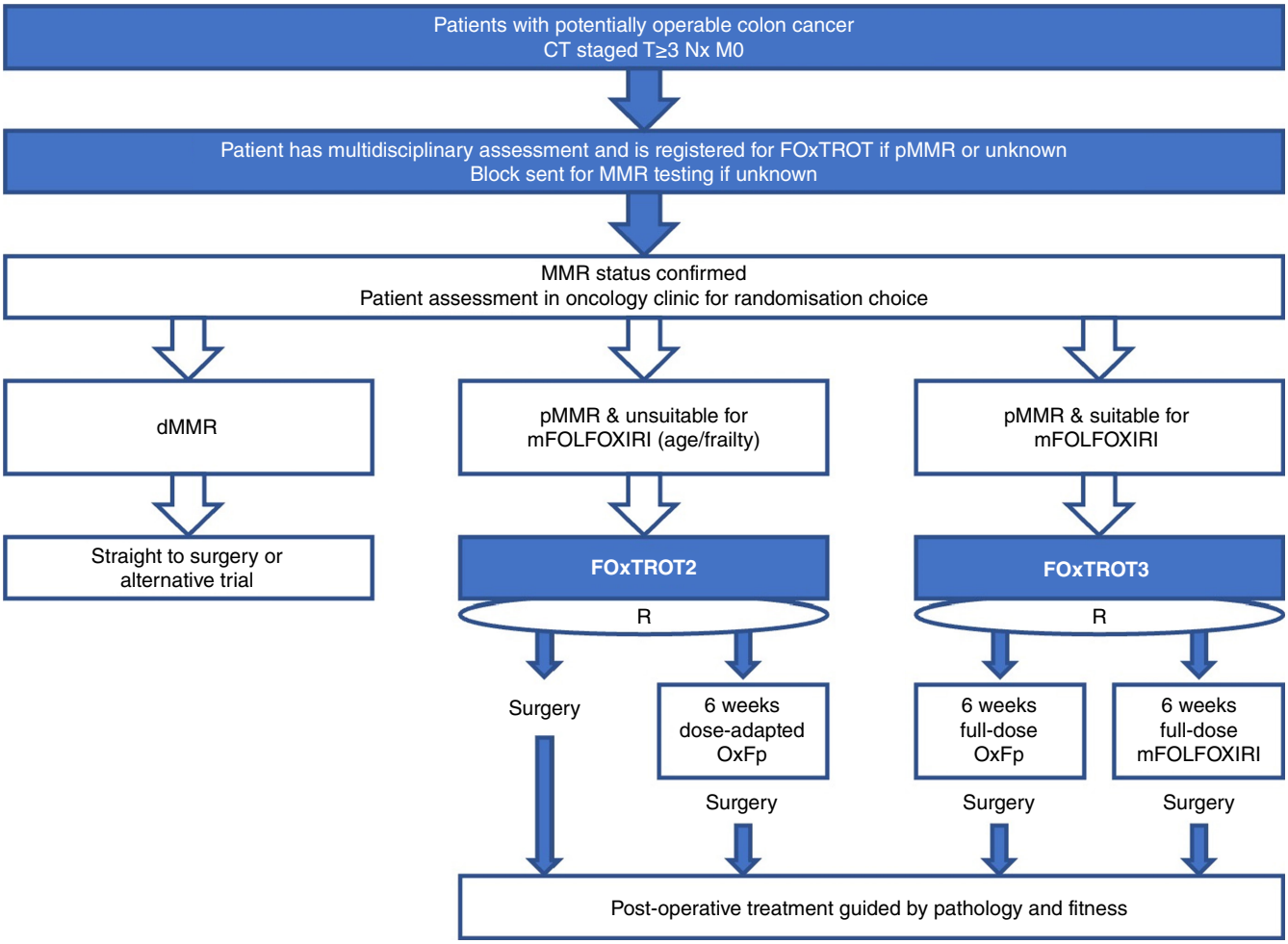

FIGURE 1 The FOxTROT platform. Patients who meet the eligibility criteria for the FOxTROT platform will be assessed for trial suitability. Patients with mismatch repair deficient (dMMR) colon cancer are not eligible for FOxTROT2 or FOxTROT3 and so will proceed to surgery or enter an alternative trial. Patient age and the presence of frailty or comorbidities will determine whether to recruit patients to FOxTROT2 or FOxTROT3. CT, computed tomography; mFOLFOXIRI, modified FOLFOXIRI (5-fluorouracil, oxaliplatin, irinotecan); OxFp, oxaliplatin and fluoropyrimidine; pMMR, mismatch repair proficient.

3 years postrandomization is higher in those who received mFOLFOXIRI compared with those who received OxFp. The null hypothesis is that there is no difference in the proportion of patients alive and disease free at 3 years postrandomization between the groups.

Recruitment

The recruitment pathway is summarized in Figure 2. Potential participants will be identified by the colorectal multidisciplinary team and invited for a registration visit. The registration visit will comprise assessment of eligibility, identification of the most suitable FOxTROT trial, provision of a patient information sheet and obtaining written consent for trial registration. Registration may then be undertaken via the Leeds Clinical Trials Research Unit (CTRU) automated 24-h registration and randomization system.

Participants with a left-sided primary tumour location (PTL) may proceed to randomization, whereas in those with a right-sided PTL, MMR/microsatellite instability (MSI) testing must be performed before proceeding. Central MMR testing is offered as part of the FOxTROT platform.

Over a 5-year period, 759 and 873 patients will be recruited to FOxTROT2 and FOxTROT3, respectively. We recognize that the rate of recruitment will vary during the first year, but thereafter the target rate will be 14 and 16 patients per month, respectively.

Eligibility criteria

The eligibility criteria for registration into the FOxTROT platform are as follows:

- biopsy-confirmed adenocarcinoma of the colon (or upper rectum if too high for radiotherapy); high grade dysplasia is acceptable with unequivocal radiological evidence of invasive cancer (patients with synchronous tumours are eligible, if the most advanced tumour meets the criteria above);
- radiological stage T3-4, N0-2, M0;

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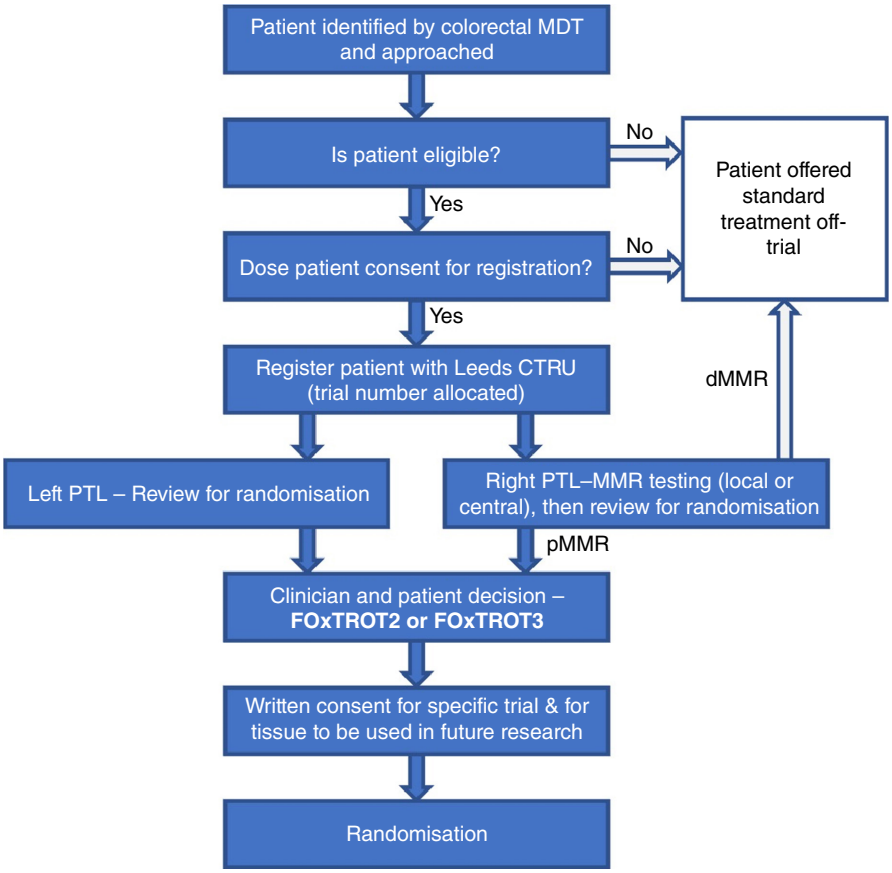

FIGURE 2 Recruitment pathway. All patients considered for the FOxTROT platform will progress through these steps. Patients who are ineligible or do not consent to participation will be offered the current treatment standard off-trial. Mismatch repair (MMR) testing is mandated for all patients with a right-sided primary tumour location (PTL) and this may be undertaken locally or via central testing. CTRU, Leeds Clinical Trials Research Unit; dMMR, mismatch repair deficient; pMMR, mismatch repair proficient.

TABLE 1 Guidance for trial suitability and dose selection.

	Age < 70 years	Age 70–74 years	Age ≥ 75 years
No frailty	FOxTROT3	FOxTROT2 100% dose	FOxTROT2 80% dose
Mild frailty or minor comorbidity	FOxTROT2 100% dose	FOxTROT2 80% dose	FOxTROT2 80% dose
Significant frailty or comorbidity	FOxTROT2 80% dose	FOxTROT2 80% dose	Clinical team to judge whether patient fit for surgery and chemotherapy

- patient being treated with curative intent;
- tumour tissue available for MMR/MSI testing (local or central);
- age ≥ 18 years at the time of registration;
- patient able and willing to provide written informed consent for the study.

Further study-specific eligibility criteria for FOxTROT2 and FOxTROT3 are broadly similar and include adequate haematological, biliary and renal function and an agreement to avoid pregnancy and/or use reliable contraception throughout and beyond treatment. Crucially, patients with dMMR or MSI-high (MSI-H) status or untreated colonic obstruction will be excluded from the studies. Those who present as an emergency with bowel obstruction are eligible, providing the obstruction is first relieved by a defunctioning stoma or colonic stent. The full list of eligibility criteria for registration and randomization can be found in the study protocols, which will soon be available on the ISRCTN registry (ISRCTN83842641).

Patient age, frailty and comorbidities will be used to determine whether treatment with mFOLFOXIRI is appropriate and whether recruitment to FOxTROT2 or FOxTROT3 is most suitable. Given the lack of a validated tool for determining whether a patient may tolerate mFOLFOXIRI, we have provided guidance to support the treating oncologist in making this decision (Table 1). We recommend the use of the Rockwood Clinical Frailty Scale to further guide this decision [6].

Randomization

Participants in both FOxTROT2 and FOxTROT3 will be randomly allocated (1:2) to either the control or intervention arm. Randomization will be performed using a computer-generated minimization program that incorporates a random element, which will ensure a balance of the following characteristics: T stage, PTL, presence of uncertain nodules on CT, age group and trial site. Furthermore,

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intended chemotherapy dose will be balanced between groups in FOxTROT2 and planned duration of perioperative chemotherapy in FOxTROT3. Prior to randomization, all patients should be deemed eligible, have completed baseline questionnaires and have provided written consent. The FOxTROT 24-h web portal should be used to perform randomization.

Interventions

In FOxTROT2, the control group will proceed STS, whereas the intervention group will receive 6 weeks of OxFp chemotherapy prior to surgery. In FOxTROT3, both groups will receive 6 weeks of NAC; the control group will receive OxFp, whereas the intervention group will receive mFOLFOXIRI (Figure 1). We recommend that DPYD germline mutation testing is performed in all patients to guide chemotherapy dosing and in some cases whether to allow participation at all.

In both trials, the treating oncologist is able to choose between giving 5FU or capecitabine. In FOxTROT2, the treating oncologist is also able to choose between giving full or reduced dose (80%) NAC. These decisions should be made when considering an individual patient's clinical context. Subsequent NAC dose reductions are permitted within the trials, up to a maximum of 20%. If further reductions are required, the patient should stop NAC and proceed to surgery. Likewise, dose delays are also permitted, up to a maximum of 2 weeks. If further delays are required, then the patient should stop NAC and proceed to surgery.

Given that OxFp is well established in routine practice, we encourage centres to follow local policy when using this regimen in the neoadjuvant setting. However, we have provided specific guidance on how to deliver neoadjuvant mFOLFOXIRI (Table 2) based upon the regimen most validated in metastatic colorectal cancer [7].

In participants receiving NAC, surgery should be scheduled between 21 and 35 days following the last dose of chemotherapy. If receiving 5FU, this interval starts following the completion of the final 5FU infusion, whereas for those receiving capecitabine the interval starts following the final dose of capecitabine. If any delays are encountered during the NAC phase, the surgical date should be pushed back to maintain the same chemotherapy–surgery interval. However, if the interval exceeds 35 days irrespective of earlier delays, the case should be discussed with the CTRU.

Details regarding the surgical management of participants within the FOxTROT platform are beyond the scope of these protocols, and this aspect of treatment should be managed by local specialist teams. However, we do require surgical teams to complete an operation note, hospital discharge letter and record the following details for the purposes of the FOxTROT platform: whether macroscopic tumour clearance was achieved, surgical/postoperative complications and length of hospital stay.

All participants should be reviewed by their oncologist within 4–8 weeks of surgery to discuss whether to proceed with AC. In FOxTROT2, given the variation in use of AC in this patient group and uncertainty around how clinicians may interpret the response to NAC, we have not mandated the use of AC. However, given that the aim of FOxTROT3 is to assess the role of intensified chemotherapy, all patients in this trial should receive AC. Participants who received OxFp NAC should continue this treatment postoperatively, whereas in those who were randomized to receive mFOLFOXIRI, the treating oncologist may choose between further mFOLFOXIRI or switching to OxFp. The treating oncologist is also permitted to choose between 6 or 18 weeks of AC. However, giving 18 weeks of AC (i.e. 6 months of perioperative chemotherapy) will be considered off-trial and should therefore be restricted to OxFp only as is the current standard of care.

Outcomes

The primary outcome in FOxTROT2 is 3-year DFS. FOxTROT1 established TRG as an effective surrogate endpoint that provides an early indication of longer-term cancer outcomes [3]. Therefore, in FOxTROT3, TRG (using the modified Dworak system [8]) and 3-year DFS are hierarchical co-primary endpoints, with 3-year DFS only considered a primary endpoint if a significant TRG result is observed. In the absence of a significant TRG result, 3-year DFS will be considered a secondary endpoint.

Secondary outcomes in both FOxTROT2 and FOxTROT3 include: tumour regression score, histopathological endpoints (tumour cell density, maximum tumour size, depth of invasion, apical lymph node involvement, overall lymph node involvement, peritoneal involvement and R1/R2 resection rate), short-term efficacy endpoints [rate of downstaging, minimal residual disease by circulating tumour DNA (ctDNA) and ctDNA alterations during NAC], safety and toxicity, cancer-specific survival, overall survival, surgical outcomes and patient-reported outcomes (PROs). PROs will be assessed using EQ-5D-5 L [9], EORTC QLQ-C30 [10] and QLQ-CR29 [11] and the Decision Regret Scale [12]. Comprehensive geriatric assessment (CGA) and TRG are also secondary endpoints specific to FOxTROT2.

TABLE 2 mFOLFOXIRI regimen (IV, intravenous)

Drug	Dose	Route	Diluent	Duration
Irinotecan	165 mg/m^2	IV infusion	250 mL 0.9% sodium chloride	30 min
Oxaliplatin	85 mg/m^2	IV infusion	250 mL 5% glucose	2 h
Folinic acid	350 mg	IV infusion	250 mL 5% glucose	2 h
5-fluorouracil	3200 mg/m^2	Continuous IV infusion	0.9% sodium chloride	46 h

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Sample size

Independent sample sizes have been calculated for each primary endpoint: FOxTROT2 (3-year DFS), FOxTROT3 (TRG) and FOxTROT3 (3-year DFS).

We hypothesized that in FOxTROT2, NAC would improve 2-year DFS from 70% to 76.5%. Assuming an exponential distribution, the 3-year DFS is estimated to be 58.6% in the STS group and hypothesized to improve to 66.9% in the NAC group, equating to an 8.3% increase in 3-year DFS (hazard ratio = 0.75).

In FOxTROT3 we hypothesized that the use of mFOLFOXIRI over OxFp will reduce the proportion of participants without TRG pathological response from 26.6% to 19.6%, equivalent to an odds ratio of 0.655, which is assumed to be reflected in similar improvements in each category under the proportional odds assumption. FOxTROT3 is also powered to assess DFS where it is hypothesized that the use of mFOLFOXIRI over OxFp will improve 2-year DFS from 75% to 80.5%. Assuming an exponential distribution, the 3-year DFS is estimated to be 65% in the OxFp group and hypothesized to be improved to 72.2% in the mFOLFOXIRI group, equating to an 7.2% increase in 3-year DFS (hazard ratio = 0.75).

To illustrate these expected benefits with a two-sided 5% significance level, 80% power, 2% dropout rate and 5-year recruitment and 3-year follow-up for the DFS endpoints, we calculated the following required participant sample sizes: 759 (FOxTROT2), 714 (FOxTROT3 TRG endpoint) and 873 (FOxTROT 3-year DFS endpoint). In order to assess both primary endpoints in FOxTROT3, 873 participants will be recruited.

Blinding

FOxTROT2 and FOxTROT3 are both open-label trials, with both patient and investigators aware of treatment allocation. In addition, periodic safety monitoring of unblinded data will be undertaken. Central pathology review will be performed in a blinded manner.

Data collection methods

Data will be collected at various points throughout the treatment pathways (Table 3) via electronic case report forms (eCRFs). Any assessments or follow-up beyond what is specified in Table 3 should be arranged as per routine clinical practice. Collection of a tissue block from the surgical specimen is mandated and should be sent to the central FOxTROT pathology laboratory. Similarly, anonymized CT scans should be sent for central storage. ctDNA testing is optional, but if performed, should be sent to the FOxTROT laboratory.

Monitoring

Monitoring of trials within the FOxTROT platform will be overseen by the CTRU and include on-site monitoring, sponsor audits and regulatory inspections. The CTRU will also monitor data quality and completeness, and may undertake data verification exercises. Any missing data will be sought by the CTRU until received, confirmed as unavailable or the trial is at the point of data analysis.

The trials will be overseen by an independent Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC). All adverse events (AEs) and mortalities should be reported to the DMEC, who will in turn provide yearly recommendations to the TSC regarding the continuation of each trial.

All adverse reactions (ARs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) must be reported to the CTRU within 24 h of the event using an eCRF. An assessment of causality will be undertaken by the chief investigator or designated clinical reviewer. All data relating to ARs, SARs and SUSARs will be collected by the CTRU, who will inform the DMEC.

Statistical methods

All statistical analyses will be conducted on the intention-to-treat population, where participants will be included according to the treatment to which they were randomized regardless of eligibility, whether they prematurely discontinued treatment or did not comply with the regimen, unless specified otherwise, using a two-sided 5% significance level. Safety endpoints will be analysed using the safety population, defined as all participants who receive study treatment, analysed according to the treatment received. Final analyses of endpoints will only be undertaken when all randomized participants have reached the primary endpoint. However, planned interim analyses will assess feasibility, safety, tolerance of NAC and accuracy of radiological staging.

In FOxTROT2, the primary endpoint of 3-year DFS will be assessed using Cox proportional hazards regression and presented using Kaplan–Meier estimates of survival. In FOxTROT3, the primary endpoint of TRG will be assessed using ordinal logistic regression. Three-year DFS will be assessed in FOxTROT3 as a co-primary endpoint if a significant TRG result is obtained and will be conducted as per DFS analysis in FOxTROT2.

Secondary endpoints (specified above) will be assessed according to data type. Time to event, categorical and continuous secondary endpoints will be assessed using Cox proportional hazards, logistic regression and linear regression models, respectively. A full statistical analysis plan will be written before any analysis is undertaken.

ETHICS AND DISSEMINATION

Research ethics approval

FOxTROT2 (protocol version 3.0, 19 November 2021) and FOxTROT3 (protocol version 1.0, 17 November 2021) have received UK ethical approval from a central research ethics committee (REC; 21/SC/0277)

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TABLE 3 Assessment schedule.

	Preregistration	Prerandomization	Prior to starting NAC	Prior to each NAC cycle	Post-NAC	Postsurgery	AC review	Prior to each AC cycle	1 year postrandomization	3 years postrandomization
Consent	X	X								
Histological confirmation	X									
CT[a]	X				X					X
MMR/MSI testing (right)		X								
MMR/MSI testing (left)[b]		X								
Clinical review		X	X	X	X	X	X	X		
Blood tests[c]		X	X	X				X		
ctDNA[d]		X		X	X		X		X	
CEA		X								
Pregnancy test[e]		X								
Colonoscopy or sigmoidoscopy	X									
CFS		X					X			
Geriatric assessment[f]		X					X			
PROs		X			X		X		X	X
Adverse event reporting				X	X					
Surgical complication reporting						X				

Abbreviations: AC, adjuvant chemotherapy; CEA, carcinoembryonic antigen; CFS, (Rockwood) clinical frailty score; ctDNA, circulating tumour DNA; MMR, mismatch repair; MSI, microsatellite instability; NAC, neoadjuvant chemotherapy; PROs, patient reported outcomes.

[a]CT should include chest, abdomen and pelvis.

[b]MMR/MSI testing is not mandated for patients with left-sided primary tumour location but is strongly encouraged.

[c]Blood tests to include full blood count, urea and electrolytes and liver function tests.

[d]ctDNA testing is optional and requires additional patient consent.

[e]Only for women of childbearing potential.

[f]FOxTROT2 only.

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Consent

Written consent is required for all participants prior to registration and randomization. All patients are given the opportunity to ask questions, have the right to refuse entry to the trial and may withdraw at a later date without having to justify this decision or prejudicing their future care. Remote consenting is permitted within the FOxTROT platform if preferred by the patient or in-person consent is not feasible.

Confidentiality

All trial documentation will be kept strictly confidential within the CTRU in accordance with the 2018 Data Protection Act. Consent forms (including participants' names) will be sent to the CTRU via encrypted electronic transfer, whereas other documentation will be sent with a coded trial number. Any medical records relating to trial participation will be held according to local policy.

Following completion of the trials, all data and the Trial Master File will be securely archived by the CTRU for a minimum of 25 years. Data at individual sites will either be securely archived or destroyed in a confidential manner, with support from the sponsor.

Access to data

Access to trial data will available on reasonable request. All requests will be reviewed by relevant stakeholders, based on the principles of a controlled access approach. Requests to access data should be made to ctru-dataaccess@leeds.ac.uk in the first instance. In addition to providing default access to participating sites, additional access may be granted to facilitate on-site monitoring, sponsor audits, regulatory inspections, DMEC safety and ethical assessments, and data verification exercises.

Dissemination policy

Any manuscripts detailing the results of FOxTROT2 or FOxTROT3 will be prepared by the Trial Management Group (TMG) and published in peer-reviewed academic journals. We will follow a corporate authorship policy, with authors listed under 'The FOxTROT Collaborative Group'. Any secondary publications related to the results of either trial may be published using a named authorship model, but only when approved by the TMG. All publications arising from these trials will acknowledge funding from Yorkshire Cancer Research and be submitted to the Europe PubMed Central Database.

Trial status

FOxTROT2 opened to recruitment on 7 February 2022 and at the time of submission has randomized 14 participants from 25 centres. FOxTROT3 opened to recruitment on 10 May 2022 and at the time of submission has randomised 17 participants from nine centres. Both trials are currently adhering to v3.0 of the master protocol for the FOxTROT platform. FOxTROT2 is adhering to v3.0 of the study-specific protocol and FOxTROT3 is adhering to v1.0 of the study-specific protocol.

DISCUSSION

FOxTROT1 has established a new standard of care for treating locally advanced but resectable CC [3]. Moving systemic treatment to the neoadjuvant setting represents a radical change to a previously well-established management pathway; hence, there is a need to refine our approach to using NAC to ensure maximum benefit and avoidance of unnecessary toxicity. Together, FOxTROT2 and FOxTROT3 represent the foundations of the FOxTROT platform, a core part of our long-term strategy for undertaking clinical and translational research relating to neoadjuvant treatment in CC.

CC is primarily a disease of older people, with the majority of diagnoses made in adults over the age of 70 [2]. Furthermore, more than half of 70-year-olds suffer from multimorbidity [13] and at least 10% suffer from frailty [14]. Whilst comparable clinical benefits were seen in FOxTROT1, older adults were poorly represented in the trial population as a whole [3]. In addition, this group of participants is likely to have comprised the fittest older adults and is therefore not reflective of the comorbidities and frailty seen in the wider patient population. We currently do not know for certain whether older adults or those with frailty benefit from NAC. It is possible that NAC may cause toxicity that precludes surgery, does not improve survival outcomes or significantly impairs quality of life in this group. Therefore, to address these important questions, FOxTROT2 has been designed specifically for older adults and those with frailty to provide definitive evidence on the role of NAC in these groups. We have successfully delivered two other large clinical trials in older patients with gastrointestinal cancers and have found this population to be enthusiastic towards trial participation [15, 16]. Furthermore, we have adapted the CGA tool used in these trials for use in FOxTROT2. Exploratory work will be undertaken to determine the value of this CGA as a tool for identifying frailty and those who may benefit from a dose-adapted NAC approach.

One of the key findings in FOxTROT1 was the association between early tumour response and greater long-term survival outcomes [3]. Hence, aiming to induce greater early tumour responses using more intensive chemotherapy should be investigated. There is good evidence for the use of mFOLFOXIRI in treating metastatic colorectal cancer, and patients under the age of 70 appeared to tolerate this treatment well [7, 17]. Therefore, FOxTROT3 has been designed to provide definitive evidence on whether the benefits of triplet chemotherapy translate to the neoadjuvant setting and produce higher rates of early tumour response.

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FOxTROT1 was delivered in the UK, Denmark and Sweden; likewise, the FOxTROT platform will be delivered from international centres across a network of multidisciplinary FOxTROT collaborators.

Future comparisons within the FOxTROT platform are planned. FOxTROT4 will commence in 2023 and test the use of targeted neoadjuvant treatments in patients with *BRAF*-mutant CC. Other comparisons will include neoadjuvant immunotherapy for patients with dMMR CC and the use of ctDNA to guide postoperative treatment decisions. FOxTROT2 and FOxTROT3 represent the start of a long-term vision for enhancing neoadjuvant treatment in CC and ultimately optimizing patient care.

AUTHOR CONTRIBUTIONS

Concept & Methodology: ZC, DAC, DM, JS; Writing & Review: JRP, CJMW, ZC, DAC, JCG, DM, JS.

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CONFLICTS OF INTEREST STATEMENT

CJMW has received speaker fees from Roche Diagnostics, Merck Serono and Servier, travel expenses from Ipsen and institutional funding from Roche Diagnostics. ZC has received institutional funding from Yorkshire Cancer Research. DAC has received institutional funding from Yorkshire Cancer Research. JS has received speaker fees from Merck Serono, Pierre Fabre and Servier, and has acted in an advisory/consultancy role for Astra-Zeneca, Merck-Serono, Pierre Fabre, Zentalis, Seagen and Elevate Oncology. JRP has no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

TRIAL SPONSOR

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The role of the sponsor and funders, and the composition, roles and responsibilities of the trial coordinating centre, steering committee, endpoint adjudication committee, data management team are detailed in the FOxTROT Master Protocol (version 3.0, 19 November 2021), available from the corresponding author.

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