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REVIEW

## FOxTROT2: innovative trial design to evaluate the role of neoadjuvant chemotherapy for treating locally advanced colon cancer in older adults or those with frailty

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Treating older adults with cancer is increasingly important in modern oncology practice. However, we currently lack the high-quality evidence needed to guide optimal management of this heterogeneous group. Principally, historic under-recruitment of older adults to clinical trials limits our understanding of how existing evidence can be applied to this group. Such uncertainty is particularly prevalent in the management of colon cancer (CC). With CC being most common in older adults, many patients also suffer from frailty, which is recognised as being strongly associated with poor clinical outcomes. Conducting clinical trials in older adults presents several major challenges, many of which impact the clinical relevance of results to a real-world population. When considering this heterogeneous group, it may be difficult to define the target population, recruit participants effectively, choose an appropriate trial design, and ensure participants remain engaged with the trial during follow-up. Furthermore, after overcoming these challenges, clinical trials tend to enrol highly selected patient cohorts that comprise only the fittest older patients, which are not representative of the wider population. FOxTROT1 was the first phase III randomised controlled trial to illustrate the benefit of neoadjuvant chemotherapy (NAC) in the treatment of CC. Patients receiving NAC had greater 2-year disease-free survival compared to those proceeding straight to surgery. Outcomes for older adults in FOxTROT1 were similarly impressive when compared to their younger counterparts. Yet, this group inevitably represents a fitter subgroup of the older patient population. FOxTROT2 has been designed to investigate NAC in a full range of older adults with CC, including those with frailty. In this review, we describe the key challenges to conducting a robust clinical trial in this heterogeneous patient group, highlight our strategies for overcoming these challenges in FOxTROT2, and explain how we hope to provide clarity on the optimal treatment of CC in older adults.

**Key words:** colon cancer, neoadjuvant chemotherapy, older age, frailty, clinical trial

### INTRODUCTION

Treating older adults and those with frailty is core to modern oncology and will only increase in importance over time.<sup>1</sup> Recognising older patients with cancer as a distinct cohort, for whom the balance of benefit and risk of treatment may differ, will allow more tailored and individualised care.<sup>2</sup> The evidence base for treating older adults with cancer is limited by under-representation in clinical trials, with many challenges that have precluded high-quality research and the development of separate clinical

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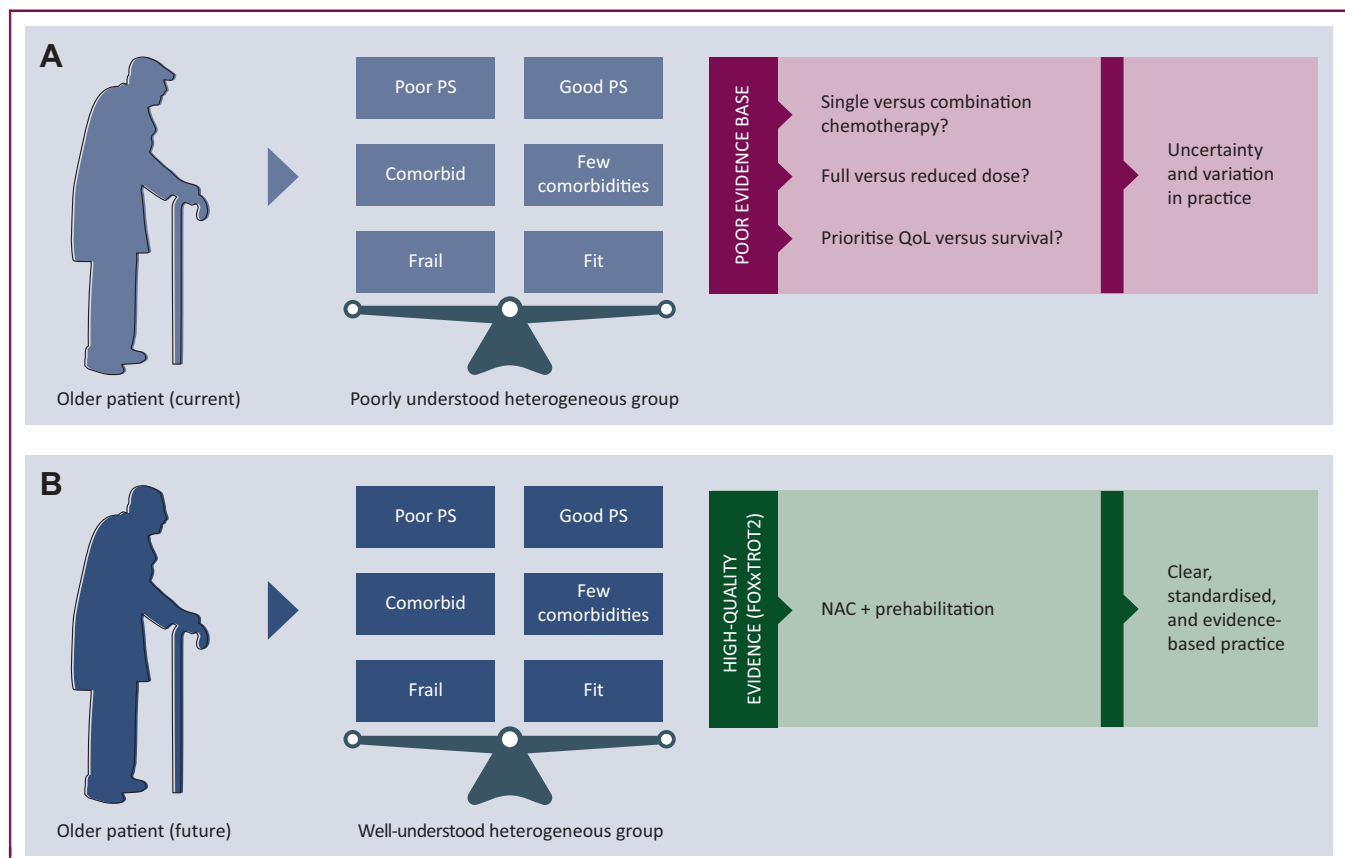
guidelines for this group.<sup>3</sup> Here, we discuss the challenges of improving the evidence base for cancer treatment in older people and describe our strategies for the upcoming FOxTROT2 trial of neoadjuvant chemotherapy (NAC) for locally advanced but resectable colon cancer (CC). Our vision for the future of treating locally advanced CC in older patients is illustrated in Figure 1.

### NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED COLON CANCER

NAC refers to the use of systemic anticancer treatments before surgical resection and is increasingly utilised in multiple tumour types.<sup>4-6</sup> The potential advantages of NAC include tumour downstaging, higher rates of complete surgical clearance, early treatment of micrometastases, reduced cancer-related systemic inflammation, lower toxicity due to shorter durations of chemotherapy before and after surgery, and a higher proportion of patients receiving systemic treatment [as often patients are too frail following surgical intervention to receive adjuvant chemotherapy (AC)]. Unlike with AC, sensitivity to NAC can be directly observed through a clinical, radiological, or histological response, and can influence post-operative risk stratification and treatment decisions. NAC also provides an opportunity to provide treatment while optimising pre-surgical health to improve

operative outcomes, a strategy known as ‘prehabilitation’. Several reports have illustrated the role of prehabilitation in improving mortality outcomes, although the exact design and implementation of these programmes remain inconsistent.<sup>7-9</sup> Potential limitations of NAC include the need to select patients using radiological parameters, risk of tumour progression during the neoadjuvant phase, and chemotherapy toxicity, which may delay surgical intervention or even lead to the disease becoming unresectable. Therefore, the risks and benefits of delivering NAC need to be considered for individual patients.

FOxTROT1 was the first randomised trial to test NAC in locally advanced but resectable CC.<sup>10</sup> Here, 6 weeks of chemotherapy with oxaliplatin and 5-fluorouracil (5-FU) given pre-operatively, followed by completion of chemotherapy post-operatively, was compared with the standard sequence of surgery followed by AC. The trial met the primary endpoint of reduced residual disease or cancer recurrence at 2 years for NAC, with no safety concerns. NAC was also associated with improved surgical clearance, fewer surgical complications, and significant tumour and nodal downstaging. Furthermore, FOxTROT1 provided evidence for prognostic molecular stratification, with mismatch repair deficient (dMMR) status associated with a lack of tumour regression and no improvement in 2-year recurrence rate.



**Figure 1. Vision for treating locally advanced colon cancer (CC) in older adults.**

(A) Older adults with CC are a poorly understood heterogeneous group. The evidence base for treating older adults with CC is limited, leading to significant uncertainty and variation in clinical practice. (B) FOxTROT2 will provide high-quality evidence for the role of NAC for treating CC in older adults and will illustrate in detail the heterogeneity and unique needs of the older patient population. Establishing NAC as a standard treatment for older patients with CC will also provide the opportunity for prehabilitation. NAC, neoadjuvant chemotherapy; PS, performance status.

## COLON CANCER IS PRIMARILY A DISEASE OF OLDER PEOPLE

CC is the is the fourth most common cancer in Europe, with over 250 000 new cases and almost 160 000 deaths each year.<sup>11</sup> In Europe, most patients with CC are diagnosed over the age of 70 years, an age at which more than half of adults suffer from multimorbidity<sup>12</sup> and over 10% experience frailty.<sup>13</sup> Additionally, the incidence of CC is increasing, and by 2040 it is estimated that 70% of all CC diagnoses will be made in adults >70 years old.<sup>11</sup> Nevertheless, there is limited evidence to guide optimal management of CC in older adults. The use of adjuvant 5-FU chemotherapy in older adults with CC is based on just a single meta-analysis.<sup>14</sup> In contrast to younger patients, the benefit of additional oxalipatin is unproven and not routinely offered in older adults.<sup>15</sup> Crucially, we also have a limited understanding of how chemotherapy impacts quality of life (QoL) in older CC patients, with just a single review describing comparable patient-reported outcomes (PROs) between age groups.<sup>16</sup>

AC is often omitted in older patients and those with frailty because the potential adverse effects outweigh the benefits of cancer control.<sup>2,17,18</sup> Furthermore, the impact of adverse effects is exacerbated by the prolonged course of AC following the debilitating effects of surgery. A shorter course of chemotherapy (assuming a comparable benefit) before surgery may overcome some of these obstacles.

## IMPACT OF FRAILITY IN THE COLON CANCER POPULATION

Frailty is a state of vulnerability characterised by poor resolution of homeostasis following a stressor, and/or the result of cumulative decline across multiple physiological systems as a consequence of biological ageing. Frailty is associated with poor clinical outcomes, longer hospital admissions, greater functional needs upon discharge,<sup>19-21</sup> long-term disability, loss of autonomy, and mortality.

Frailty presents several challenges in the treatment of CC. Surgery for CC represents a significant physiological stressor, which is associated with an increased risk of post-operative complications, prolonged hospital stay, and hospital readmission in people with frailty.<sup>22</sup> Poor surgical recovery secondary to frailty may then preclude the use of AC entirely, thereby limiting the potential for curative treatment. This may in part explain why fewer patients over the age of 70 years receive AC and why there is marked geographical variation seen throughout the UK in its provision.<sup>23</sup> Finally, in those who do receive chemotherapy, patients with frailty are at greater risk of treatment toxicity.<sup>24</sup> Nevertheless, a unified consensus on how to assess frailty and reliably identify this at-risk patient population is lacking.<sup>24,25</sup>

## NEOADJUVANT CHEMOTHERAPY IN OLDER PATIENTS WITH COLON CANCER

While modern cancer clinical trials rarely set upper age limits, adults >70 years of age are poorly represented.<sup>26</sup> In FOxTROT1, nearly a quarter of those recruited were >70

years old, but were predominantly of good performance status. However, comparable effects of NAC on 2-year recurrence (16.9% versus 16.8% for those aged >70 years and the overall study population, respectively) and tumour regression (61.5% versus 65.3%, respectively) were seen in subgroup analysis.<sup>10</sup> Beyond CC, the benefit of NAC in older patients has been reported in other disease sites, including ovarian and pancreatic cancer.<sup>27,28</sup> Neoadjuvant (chemo) radiotherapy is also well established for older patients with locally advanced rectal cancer.<sup>29,30</sup> FOxTROT2 will investigate the role of NAC for treating locally advanced CC in older adults and those with frailty.

## THE CHALLENGES OF CARRYING OUT CLINICAL TRIALS IN OLDER ADULTS AND THOSE WITH FRAILITY

### *Defining the target population*

Older patients represent a heterogeneous population with various comorbidities, disabilities, and geriatric syndromes, all of which produce varying degrees of vulnerability to the side-effects of cancer treatment. While age has traditionally been used as a simple surrogate marker for frailty, there is inconsistency in the definition of old age, ranging from 65 to 80 years.<sup>31</sup> Furthermore, overall health is recognised as superior to age for predicting chemotherapy tolerance,<sup>32</sup> indicating the need for a holistic and individualised assessment of frailty and overall health status. Frailty assessments represent a method of evaluating a person's overall health status and are increasingly utilised and acceptable among patients and their clinicians across a range of medical and surgical specialties.<sup>33</sup> However, it is unclear which assessment model is optimal for identifying frailty in cancer patients and therefore who to recruit to clinical trials.<sup>25</sup> Broadly, there are two recognised approaches to frailty assessment: the cumulative deficit model, which describes frailty as a state of accumulated impairments, and the frailty phenotype model that identifies frailty as a syndrome of low-level physical activity, weight loss, weakness and slowness, and poor endurance.<sup>24</sup>

### *Recruitment*

Older adults are often under-represented in clinical trials.<sup>26</sup> This presents a major challenge in developing evidence-based guidance for cancer treatment in older people.<sup>3</sup> Consequently, we also lack real-world data for treating older cancer patients.<sup>34</sup> Trial participation is particularly low in adults from the following groups: >85 years old, existing frailty or dementia, ethnic minorities, and deprived communities.<sup>35-38</sup> There are myriad reasons for poor recruitment of older adults in clinical research, including restrictive eligibility criteria, clinician scepticism or biases, patients feeling too unwell to participate, the burden of existing medical appointments, or logistical issues (e.g. transport or communication barriers).<sup>39</sup>

Current evidence for treating older cancer patients is usually drawn from subgroup analyses which are often statistically under-powered to provide definitive findings.

Furthermore, treatment effects are more heterogeneous in older patients, and thus more challenging to evaluate. Under-recruitment of older patients leads to the curation of highly selective patient groups, often comprising the fittest older patients. This selection bias may consequently limit the generalisability of findings to the older population as a whole. Nevertheless, we have found older adults to be enthusiastic towards trial participation, and have successfully delivered two large trials in older adults with gastrointestinal cancers.<sup>40,41</sup>

### Trial design

To overcome historic under-representation of older patients in cancer research, trials should be designed specifically for the older patient population. However, designing high-quality studies for older patients is often more complex than for younger age groups. Randomised controlled trials (RCTs) remain the gold standard for assessing treatments in older patients, but accounting for the heterogeneity of these patients can be challenging. Extensive exclusion criteria have historically limited the recruitment of older patients to trials. Therefore, it is recommended that eligibility criteria are permissive where possible to account for patient heterogeneity, in particular those relating to patient function and comorbidities.<sup>3</sup> Traditionally, cancer clinical trials have utilised fixed full-dose treatments, which may be unsuitable for older patients. With emerging evidence highlighting the equivalent benefit of lower-dose chemotherapy in certain settings,<sup>40,41</sup> dose flexibility should be encouraged within trial design to support the participation of older adults. The importance of trial co-production with patients and other stakeholders has been highlighted by the NIHR INCLUDE project and represents a crucial strategy for addressing these challenges in the under-served older population.<sup>42</sup>

Comprehensive geriatric assessment (CGA) comprises a multi-dimensional assessment of a person's medical, psycho-social, and functional capabilities and limitations, and is crucial to illustrating the heterogeneity of health needs in trial participants at baseline.<sup>43</sup> The International Society of Geriatric Oncology (SIOG) recommends CGA in patients >70 years old, with recognition that assessment by performance status is insufficient.<sup>44</sup> The limited use of CGA in clinical trials has precluded our understanding of how applicable trial findings are to the older patient population. Furthermore, whilst CGA has been shown to be feasible within the clinic,<sup>45</sup> we lack a standardised approach to this assessment in clinical trials. The European Organisation for Research and Treatment of Cancer (EORTC) has published a minimum dataset for geriatric assessment in clinical trials,<sup>46</sup> but several others have been used within the literature.<sup>47-51</sup>

### Outcome selection

While there are numerous established endpoints in oncology trials, such as overall survival and response rate, many of these may be less appropriate for older adults or those with frailty, who live with competing risks. For example, older cancer patients may die from existing

comorbidities rather than cancer relapse, and cancer treatments may cause severe toxicity and affect QoL. In the context of older age, it is conceivable that QoL may be of greater importance to patients than longevity. Therefore, appropriate outcomes should be chosen for older people and may include event-free survival or QoL. However, like many of these challenges, there is inconsistency within the literature regarding how to assess QoL.<sup>52</sup> To address this disparity, the EORTC Elderly Taskforce developed the QLQ-ELD14 module for older patients to be used to measure older patients' experience in addition to the existing QLQ-C30 questionnaire within a clinical trial setting.<sup>53</sup>

### Follow-up

Older adults and those with frailty are more likely to be lost to follow-up than younger patients, given their greater risk of death secondary to old age, comorbidities, cancer, or cancer treatment. Furthermore, accessing intensive trial follow-up may be limited by difficulties with mobility, transport, or communication. Incorporating follow-up into routine clinic appointments and the linkage of routine data from secondary care (e.g. Hospital Episode Statistics in England and Wales) and primary care electronic health records could support trial participation and reduce patient burden. Embracing digital technology to support follow-up may both alleviate appointment burden and overcome access difficulties. Furthermore, utilising digital technology may reduce costs for both the patient and the research team, facilitate greater geographical reach, limit the challenges of attending in-person appointments, empower and promote patient independence, and ultimately develop a more patient-centred trial experience.<sup>54,55</sup> However, older people experience many barriers to the routine use of digital technology, which may limit its role in clinical trials for this patient group.<sup>56</sup>

## WHAT HAVE WE LEARNED FROM OTHER TRIALS?

FOCUS-2 and GO2 are two RCTs that were specifically designed for older adults and those with frailty, providing much needed evidence for the treatment of gastrointestinal malignancies.<sup>40,41</sup> Both FOCUS-2 (metastatic colorectal cancer) and GO2 (metastatic gastro-oesophageal cancer) established the role of lower-dose chemotherapy in older patients and those with frailty. Both trials showed maintenance of clinical response but with reduced toxicity and improved QoL.

FOCUS-2 also introduced the concept of overall treatment utility (OTU), a novel composite measure designed to reflect the benefits and harms of chemotherapy in older patients. OTU was developed further in the 321GO<sup>57</sup> and GO2 studies, and now represents a useful clinical tool to support complex decision making in a vulnerable patient population. FOCUS-2, 321GO, and GO2 were also used to develop a standardised approach to CGA.

## WHAT HAVE WE PROPOSED IN FOXTROT2?

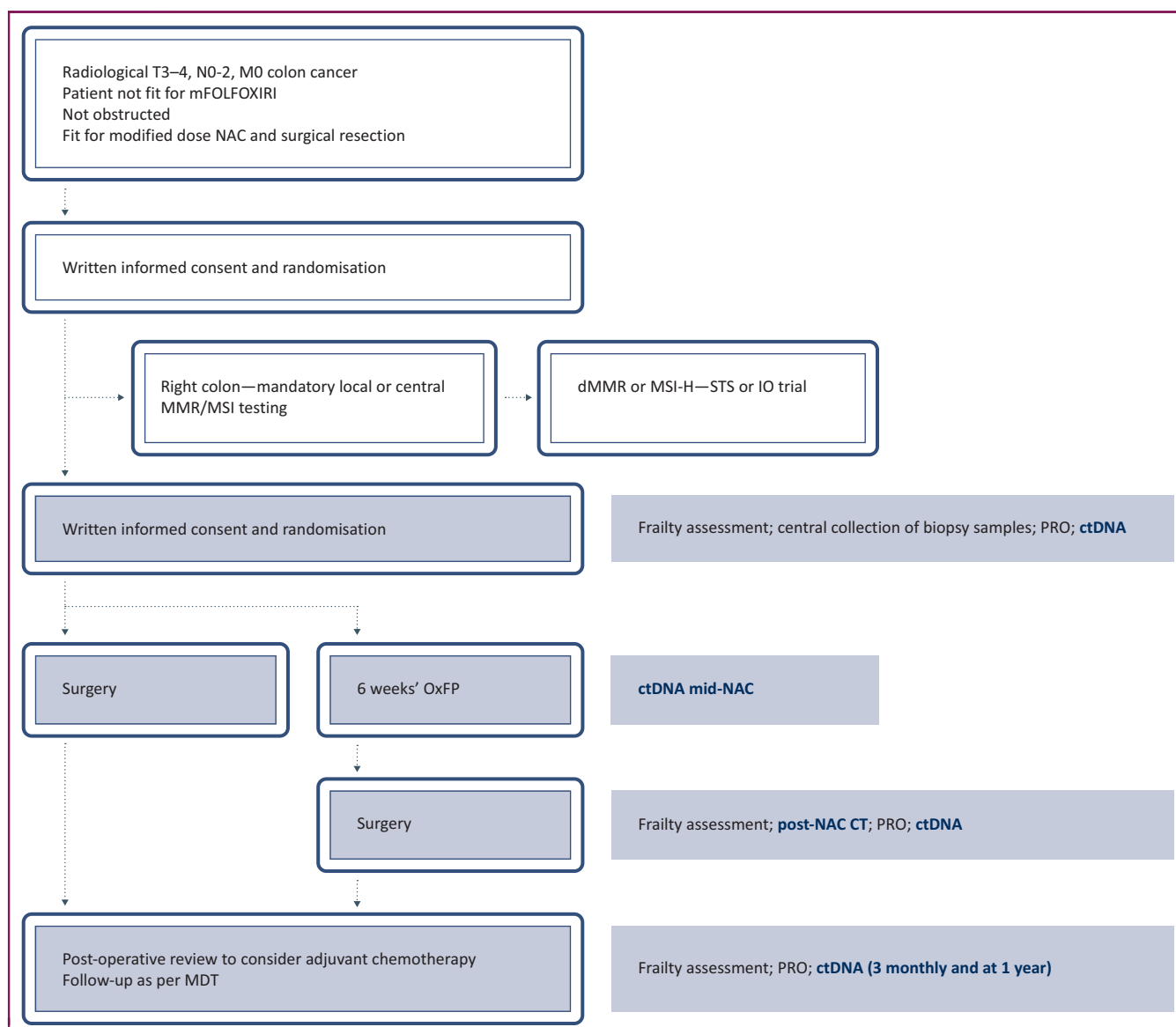
FOxTROT2 is a phase III RCT investigating the use of NAC for locally advanced CC in older adults or adults with frailty. The



primary endpoint of 3-year disease-free survival will be compared between patients receiving neoadjuvant oxaliplatin and 5-FU and those proceeding straight to surgery (Figure 2). Secondary endpoints include treatment toxicity, tumour downstaging, overall survival, surgical morbidity, PROs (including QoL), and CGA. FOCUS-2 and GO2 raised important questions around the established convention of striving for maximal tolerated dose within chemotherapy trials. Therefore, we have designed FOxTROT2 to be agile and adapt to the individual patient, offering lower-dose upfront chemotherapy as a treatment option.

Where possible, we have designed FOxTROT2 to meet the needs of older adults and address the challenges we have identified. To reliably identify our patient cohort, the eligibility criteria for FOxTROT2 were designed in

conjunction with the FOxTROT3 trial; FOxTROT3 will investigate the role of intensification of chemotherapy with modified fluorouracil/oxaliplatin/irinotecan in fit patients with locally advanced CC, a population likely to be similar to the FOxTROT1 trial. If, following clinician assessment, a patient is deemed unsuitable for triplet NAC due to frailty, they will subsequently be considered for FOxTROT2. No specific age threshold will be used in selecting patients for FOxTROT2, instead seeking the most appropriate patients based on frailty and overall health status: this advice was strongly recommended by our patient advisory group. Where possible, we have avoided stringent eligibility criteria to ensure we capture the frail population and reflect clinical practice. Within the protocol, we suggest the use of the Rockwood Clinical Frailty Scale<sup>50</sup> for a rapid assessment of



**Figure 2. FOxTROT2 trial.**

The schematic for FOxTROT2, illustrating the patient journey and treatment pathways. MMR/MSI testing is only mandated for right-sided tumours due to the majority of dMMR/MSI tumours being right-sided. Upfront MMR/MSI testing in left-sided tumours is not mandated, but is encouraged.

CT, computed tomography; ctDNA, circulating tumour DNA; dMMR, mismatch repair deficient; IO, immuno-oncology; MDT, multidisciplinary team; MSI-H, microsatellite unstable; MSS, microsatellite stable; NAC, neoadjuvant chemotherapy; OxFP, oxaliplatin and 5-fluorouracil; PRO, patient-reported outcome; STS, straight to surgery.

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

frailty, and have provided guidance on trial selection to our investigators (Table 1). To limit the impact of patient heterogeneity, we will undertake comprehensive patient profiling with appropriate subgroup analysis and statistical stratification. FOxTROT2 will also provide an opportunity to develop a valid and reproducible approach to frailty assessment, identify a well-defined cohort of patients who benefit from NAC, and promote the consistency in clinical practice that is currently lacking.<sup>23</sup>

CGA forms a fundamental part of FOxTROT2 and is carried out at baseline and pre-AC. We have adapted the CGA established in FOCUS-2, 321GO, GO2, and wider surgical practice, supporting a consistent and reproducible methodology that can be applied across different settings. Our CGA comprises the Rockwood Clinical Frailty Scale,<sup>50</sup> G8 screening tool, nurse-led assessments, and PROs—including EORTC QLQ-C30,<sup>58</sup> QLQ-ELD14,<sup>53</sup> QLQ-CR29 (with additional peripheral neuropathy item),<sup>59</sup> EQ5D,<sup>60</sup> and Decision Regret Scale<sup>61</sup>—and complies with the EORTC minimum dataset for geriatric assessment. The CGA assesses frailty according to 13 domains, each with a specific threshold for impairment: participants with impairment in three or more domains are considered to have high levels of frailty. However, the CGA is not a validated tool for decision making in this setting, and so is being conducted post-randomisation, with the final decision on trial selection made by the treating oncologist. Information from the CGA will be used during interim safety analyses to ensure that patients identified as most frail do not experience excess toxicity, and will also be presented at final analysis.

FOxTROT2 is distinct from FOCUS-2 and GO2 in several ways. FOxTROT2 will recruit patients with locally advanced CC for treatment with curative intent, whereas FOCUS-2 and GO2 treated patients in the metastatic setting. Hence, the primary treatment aims will differ, with lower tumour recurrence, higher rates of cure, and improved surgical outcomes representing greater priorities in FOxTROT2. While QoL remains a key outcome in FOxTROT2, there is a more delicate balance to be achieved with outcomes such as tumour recurrence. Furthermore, outcomes in FOxTROT2 are not mutually exclusive, with improved survival and surgical outcomes likely to enhance QoL in ways not seen in the metastatic cancer trials. Given these contrasting aims, the FOxTROT2 population will also have a different frailty status to the patients in FOCUS-2 and GO2.

All patients recruited to FOxTROT2 will be deemed fit enough to undergo both major abdominal surgery and systemic chemotherapy, whereas in FOCUS-2 and GO2, patients were only required to be suitable for chemotherapy. Therefore, the range of frailty within these trials is likely to differ. In FOxTROT2 we hope to provide greater clarity regarding the frailty status of older adults who benefit from NAC.

FOxTROT2 will provide unique opportunities to develop the evidence base through numerous translational projects. Data and specimens obtained through the trial will support identification of biomarkers across the clinical, biochemical, radiological, and pathological landscapes, including integration of circulating tumour DNA and radiomics. Furthermore, we hope to develop a robust, valid, and reproducible frailty assessment tool to support decision making in both surgical and oncological settings.

To ensure FOxTROT2 produces meaningful results for older patients, we have incorporated PROs throughout at meaningful timepoints, to collect information on QoL, toxicity, and patient preferences. PROs will be used to establish elements of frailty, stratify treatment allocation, and assess tolerance of NAC. Subsequently, PROs will be integrated into follow-up to determine the tolerability and acceptability of the overall treatment pathway of NAC, surgery, and AC. We have also designed the treatment arms to reflect the varying needs of our patients, including a stratified choice of chemotherapy dose (full dose or 80% dose) and regime (oxaliplatin and intravenous 5-FU or oxaliplatin and oral capecitabine). This flexible approach to trial design will help empower patients and promote engagement with the trial process. Choice of regime and dose are likely to vary between oncologists and patients; collecting data to illustrate this variation will provide insight into decision making for NAC and support strategies to improve consistency in practice. To further encourage participation, we have designed the follow-up programme to mirror standard practice and therefore limit patient burden.

## NEOADJUVANT IMMUNOTHERAPY IN OLDER PATIENTS WITH COLON CANCER

Recent data from the NICHE-2 study demonstrated the safety and spectacular short-term efficacy of a short course of neoadjuvant immunotherapy with nivolumab and ipilimumab in patients with locally advanced dMMR CC. Here, 95% of patients achieved a major pathological response at the time of surgery; longer-term data are awaited. The median age of participants in NICHE-2 was 60 years. This data may be of particular relevance for older adults for several reasons: dMMR status is more common in older adults with CC<sup>62</sup>; the potential for better tolerance of neoadjuvant immunotherapy compared to NAC; and looking into the future, the potential for an organ preservation strategy in those with complete response to neoadjuvant immunotherapy.

Whilst there is increasing evidence for the use of neoadjuvant immunotherapy across different tumour types,

older adults and those with frailty continue to be poorly represented in trials.<sup>63</sup> Furthermore, there are no published neoadjuvant immunotherapy trials designed specifically for older adults, meaning any conclusions are drawn from subgroup analyses. Immune checkpoint inhibitors are commonly used in the adjuvant and metastatic settings, and are well tolerated by older adults.<sup>64</sup> We would therefore recommend a dedicated study of the safety and efficacy of neoadjuvant immunotherapy in older patients and those with frailty, employing the principles discussed in this article.

## CONCLUSION

Advances in oncology mean that cancer in older patients is increasingly treatable, yet the evidence base for surgery and chemotherapy in older adults and those with frailty is lacking. We have designed the FOxTROT2 trial with the needs of older adults and those with frailty in mind, and believe that it represents a significant step in improving the evidence base for this growing population of cancer patients.

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All contributors to this manuscript are listed as authors.

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## DISCLOSURE

ZC has received grants from Celgene, MSD, Amgen, and Takeda (via institution). MS has received a grant from Yorkshire Cancer Research to support provision of a clinical trial (via institution). MB has received payment/honoraria from Laboratoires Pierre Fabre, Amgen, and Servier, is Co-lead of Audit for the National Bowe Cancer Audit (England and Wales), and author of the National Institute for Health and Care Excellence (NICE) Colorectal Cancer Guideline. JR has received grants from Bristol Meyers Squibb, Laboratoires Pierre Fabre, Servier, HUB Organoids, and Cleara Biotech (via institution), consulting fees from Bayer, Bristol Meyers Squibb, Merck-Serono, Laboratoires Pierre Fabre, and Servier (via institution), payment/honoraria from Bristol Meyers Squibb, Laboratoires Pierre Fabre, and Servier (via institution), and support for attending meetings from Servier. JR is also a member of advisory boards for the PelvEx and MEND-IT trials, and a member of the ONCODE clinical advisory board. CP has received consulting fees from Nordic Pharma (via institution). JT has received payment/honoraria from Astellas Pharma Inc., Bristol Meyers Squibb, MSD, Merck & Co., Roche, Laboratoires Pierre Fabre, Novartis, and Servier, support for attending meetings from Laboratoires Pierre Fabre, MSD, and Servier, and is a member of advisory boards for Bristol Meyers Squibb, MSD, Merck & Co., Roche, Laboratoires Pierre Fabre, Novartis, and Servier. JB has received grants from Cancer Research UK, the National Institute for Health and Care Research, Medical Research Council, and Roche,

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