2010

321GO

Three, two or one-drug chemotherapy for advanced gastroesophageal cancer: a feasibility study in frail and/or elderly patients.

Trial Protocol Version 3.0

10th February 2010

Sponsor: The University of Leeds

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Protocol Signature Page

Study title: Three, two or one-drug chemotherapy for advanced gastroesophageal cancer: a feasibility study in frail and/or elderly patients.
Protocol version: 3.0
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Approved by Chief Investigator:

(Prof. Matthew Seymour MD FRCP)

Date: 10/02/2010

Investigator's Agreement:

I have read the attached protocol entitled "321GO: Three, two or one-drug chemotherapy for advanced gastroesophageal cancer: a feasibility study in frail and/or elderly patients" (version 3.0, dated 10.02..2010 and agree to abide by all provisions set forth therein.

I agree to comply with the principles of Good Clinical Practice (GCP), the EU and GCP Directives (2001/20/EC; 2005/28/EC) and The Medicines for Human Use (Clinical Trials) Regulations and Amendment Regulations 2006 (Statutory Instrument 2006 No. 1928).

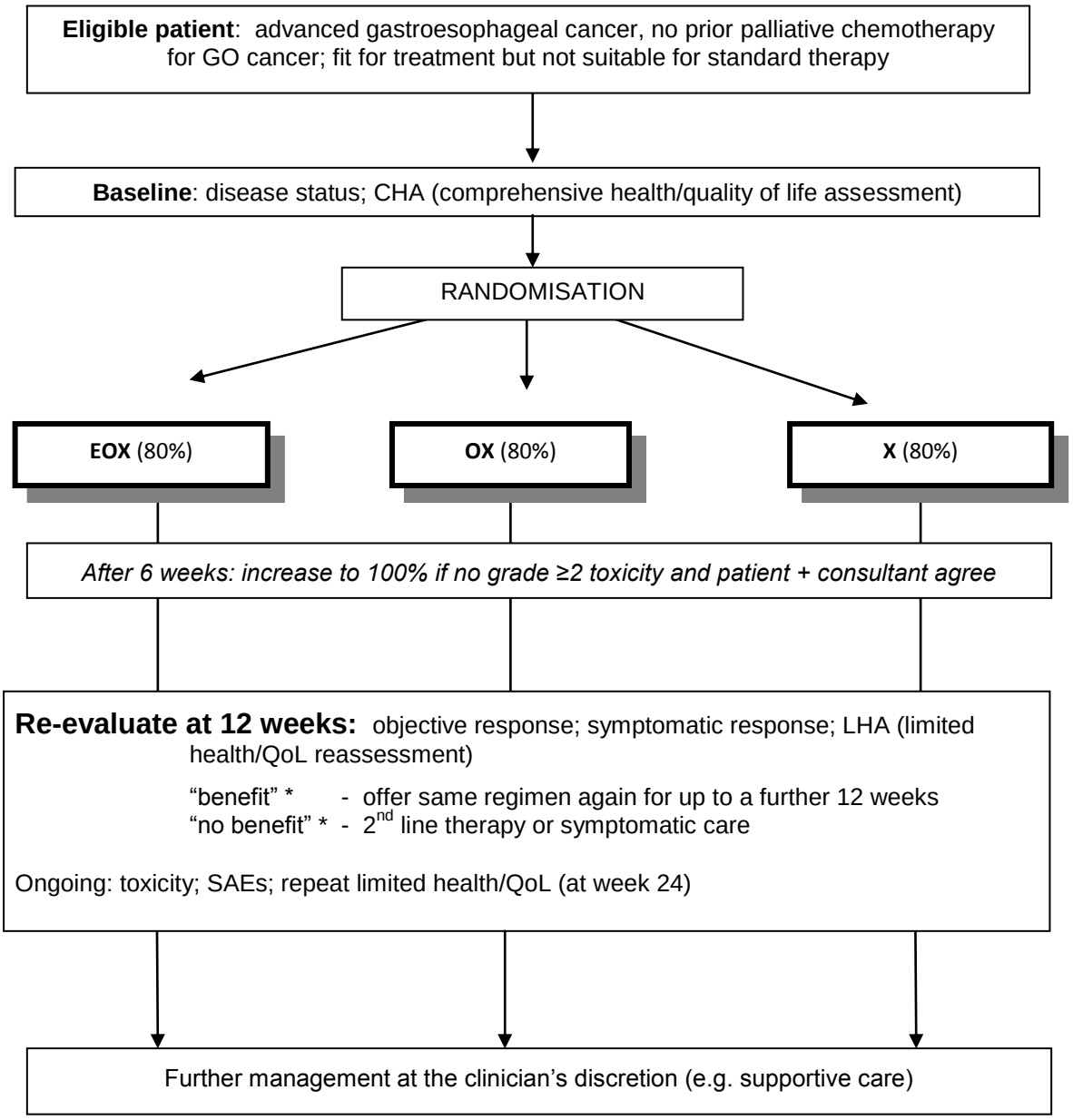
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Gastrointestinal Cancer Unit of Leeds Institute of Oncology, NHS Foundation Trust.

Signature:_____

Name of Principal Investigator:_____

Date (DD Month YYYY):_____

Trial Design



* "benefit" = no evidence of radiological progression or symptomatic deterioration
"no benefit" = either radiological progression or symptomatic deterioration

1 Trial Summary

321GO assesses gentler treatment for patients with advanced gastroesophageal (GO) cancer who are ineligible or unsuitable for full-dose combination chemotherapy because of borderline performance status, advanced age or both. The aim is to establish the feasibility of setting up a phase III randomised trial which would ultimately help provide an evidence base for this group of patients.

The trial design is modelled on FOCUS2, which recently completed successful national recruitment in a similar frail/elderly population with advanced colorectal cancer. After baseline assessments including disease measurement and a comprehensive assessment of general health and quality of life (CHA), patients will be randomised (1:1:1) to one of the following treatments:

- **EOX:** Epirubicin 40mg/m^2 d1, Oxaliplatin 104mg/m^2 d1, Capecitabine 500mg/m^2 bd x21d
- **OX:** Oxaliplatin 104mg/m^2; Capecitabine 500mg/m^2 bd x 21d.
- **X:** Capecitabine1000mg/m^2 bd d1-14, then 7 day rest.

All three treatments are given on 3-week cycles. **EOX** was developed in REAL2 and will be the control arm for the planned REAL3 trial. **OX** is the same regimen, with epirubicin omitted. **X** is the standard single-agent capecitabine regimen. In all three regimens, the starting doses, given here, are 80% of standard doses.

As in FOCUS2, patients will be assessed after 6 weeks. If no toxicity of grade ≥2 has occurred, and if the patient and clinician agree, the chemotherapy doses will then be increased to 100% standard (i.e. a 20% increase from the starting doses shown above). Treatment will continue as 3-weekly cycles for a maximum of 8 cycles. Disease status and limited general health/QoL reassessment are measured after completing the initial 12 weeks' treatment, and again at 24 weeks.

Feasibility Aims and Sample Size

Information from 321GO will be used to assess the feasibility of performing a national phase III trial, to run alongside REAL3, evaluating chemotherapy options for the elderly and/or frail population with advanced GO cancer.

Recruitment will take place over 18 months. Participating centres will be asked to monitor the total number of patients referred for treatment of advanced GO cancer during the recruitment period and to report the proportion of patients offered full-dose regimens (e.g. in REAL3 or off trial), alternative treatments, or who declined randomisation.

For patients entering 321GO, the principal outcome measure is the rate of recruitment into the trial. Secondary outcome measures include tolerability of each regimen (assessed in terms of [a] the incidence of CTCAEv3 grade ≥3 toxicities, [b] the incidence of SAEs and dose delays/reductions, and [c] the ability/willingness to dose-escalate to 100% at week 6), patients' acceptability scores, quality of life changes, nutrition and symptom control.

Introduction

In recent years there has been a welcome shift in UK cancer management. All patients with malignancy, including the frail and elderly, are now discussed in multidisciplinary teams, with site-specialised oncology expertise. Consequently most patients with advanced GO cancer are offered palliative chemotherapy.

Background

GO cancer causes 13,000 deaths per year in the UK, at a median age of 77 years. Over half of these deaths occur in patients over the age of 75.[1] The peak age of diagnosis is becoming older.[2] As a consequence of advanced age, patients commonly present with co-morbidities and reduced PS. GO cancer is also positively associated with smoking tobacco and alcohol excess which incur co-morbidities.

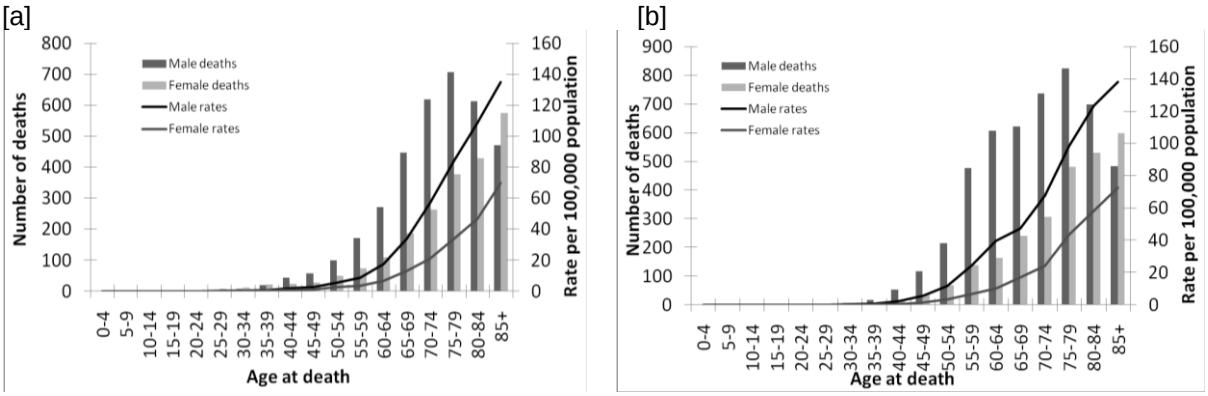


Fig 1. Age specific mortality: [a] stomach cancer [b] oesophageal cancer

Current standard treatment

Early trials of chemotherapy versus supportive care alone in GO cancer suggested approximately 6 months' prolongation of median survival (from 3-5 months to 9-12 months), with quality of life benefits.[3] Over the past 15 years a series of clinical trials in the UK and elsewhere established 3-drug regimens, typically fluoropyrimidine, platinum and anthracycline, such as "ECF" (epirubicin, cisplatin, fluorouracil). The individual contributions of the components of these 3-drug regimens are difficult to evaluate. For example, in a recent meta-analysis,[4] the benefit of epirubicin appeared modest, and it was shown to contribute to toxicities such as alopecia, neutropenia and stomatitis. Many patients are managed with a fluoropyrimidine alone, but there is a breadth of evidence from small randomised trials that the omission of a platinum agent from the palliative treatment of gastroesophageal cancer results in less effective treatment.[5,6,7,8] Phase II trials of capecitabine alone in GO cancer report response rates of 19-34% but there is no comparative data available with combination chemotherapy.[9,10]

Most recently, the NCRI trial **REAL2**[11] has defined a new option for standard treatment. This trial recruited 1002 patients, of median age 63 years of which 89% had a PS 0-1. ECF was the control arm and, in a 2x2 factorial design, FU was substituted with capecitabine ("X"), and cisplatin with oxaliplatin ("O"). In both cases efficacy was maintained,

and with the double-substitution "EOX" regimen, overall survival (OS) was significantly improved compared with ECF. EOX also has some practical advantages, avoiding inpatient admissions for cisplatin and with no necessity for central venous access. Based on these results, the next NCRI trial for fit patients with advanced GO cancer (REAL3) will use EOX as its control arm, with patients randomised to receive this regimen +/- panitumumab.

Chemotherapy in elderly and/or frail co-morbid GO patients

It is now well recognised that the ability to respond to chemotherapy is independent of age. However, chemotherapy can be affected by age-related changes in pharmacokinetics and pharmacodynamics leading to increased toxicity with doses established in younger patients.[12,13,14] Despite efforts to make the eligibility criteria for trials inclusive, there is a conspicuous mis-match between the age of patients with advanced GO cancer in the population (median >75 years) and the populations recruited to RCTs such as REAL2 (median 63 years). There is a similar but less measurable mismatch in frailty, PS and co-morbidity. This leaves uncertainty in both patient selection and choice of dose/regimen when treating frail and elderly patients.

How are elderly and and/or frail GO patients currently treated?

We audited 100 patients over 65 years of age who received palliative chemotherapy for advanced GO cancer in a single large centre (Leeds), over a 4-year period. 74% received chemotherapy regimens that would be considered non-standard for reasons of co-morbidity, renal function, PS or age alone (Appendix 3). Only 2 patients over the age of 70 received full dose 3-drug chemotherapy. A survey of non-surgical oncologists managing GO cancer across North and West Yorkshire – treating a population of over 3 million – showed no consensus over optimal regimens. It also highlighted a lack of objective health assessment tools for informing decision-making in older and less fit patients.

What is the current evidence?

This comprises analyses of the small subgroup of elderly or poor PS patients in "main-line" trials, or smaller studies aimed specifically at the frail/elderly population. A subgroup analysis of patients over 70 years of age in 3 large trials of palliative combination chemotherapy in GO cancer demonstrated that they had similar symptomatic response rates, objective response rates and survival as younger patients, without increased toxicity.[15] This is consistent with the experience in colorectal cancer.[16] However, it is important to recognise that these studies are looking at a highly selected elderly population.

Studies aimed specifically at the frail/elderly population include oxaliplatin in combination with bolus or infusional 5FU with acceptable toxicity.[17,18,19,20] A phase II study comparing the oral fluoropyrimidines S-1 and capecitabine in elderly patients with advanced gastric cancer demonstrated both agents to be active and tolerable.[21] The addition of mitomycin-C to 5FU was tested in a phase III trial with a median age of 72, but produced no survival advantage.[22]

Extrapolating from other tumour types - the FOCUS2 trial

Under-representation of elderly and/or frail patients in clinical trials has also hampered the applicability of evidence in colorectal cancer. The MRC FOCUS2 trial addressed this by specifically recruiting elderly and/or frail patients and using initially reduced doses of standard regimens including single agent capecitabine and oxaliplatin with capecitabine. Dose escalation was achieved in a proportion of patients and toxicities were acceptable.[23]

Health Assessment

In FOCUS2, a rigorous 117 point "comprehensive health assessment" tool (CHA) was applied at baseline and again at 12 and 24 weeks. It included assessment by different domains: frailty, symptoms, nutritional status, medical co-morbidity, cognitive function, mental health, activities of daily living and overall quality of life. Compliance was 100% at baseline, and 70% of available patients completed the 12-week assessment. Initial multivariable analysis, including these factors alongside conventional prognostic factors, has identified a number of baseline factors with potential predictive value for the benefit of palliative chemotherapy. [24]

The CTCAE was designed for clinician reporting; the wording for the grading of various items is technical. There is a growing interest in the use of patient-reported outcomes and health-related quality of life assessment tools to collect symptom measures directly from patients to improve the accuracy and efficiency of adverse event or toxicity reporting. The Cancer Research UK Psychosocial Oncology and Clinical Practice Research Group in Leeds have developed a chemotherapy toxicity questionnaire using the CTCAE model in patient self-report format. Within 321GO we will explore the feasibility of this method of chemotherapy toxicity reporting and how well it corresponds to the clinician/nurse assessment of patients' toxicity.

GO Tumour Types

Meta-analyses showed no significant differences in the outcome of palliative chemotherapy for GO carcinomas depending on primary site[25] or between adenocarcinoma and squamous histological types[26] All these patients will therefore be eligible for 321GO.

The need for a phase III trial

Although FOCUS2 specifically targeted the frail/elderly population in colorectal cancer, and has provided valuable evidence, we now wish to expand this approach to GO cancer. However, before embarking on such a project, we need to establish its feasibility: What proportion of GO cancer patients would be recruited? What is a realistic accrual target for a national trial? Is the FOCUS2 approach of starting at 80% of the maximum standard chemotherapy dose appropriate in GO cancer? Can a comprehensive health onco-geriatric assessment tool be applied to this population?

3 Aims

3.a Feasibility study questions:

- What rate of recruitment can be expected for a national multicentre phase III trial of this design?
- What proportion of all patients presenting with GO cancer are suitable for recruitment into a trial of this design?
- Is tolerability of each regimen acceptable for inclusion in a large phase III RCT using these reduced-dose regimens in this patient population?
- Approximately what median progression-free survival is seen in this patient population (to contribute an accurate power calculation for the phase III trial)?

3.b Proposed Phase III trial questions:

- Do patients in this population benefit from chemotherapy – including modern combination chemotherapy – at modestly reduced starting doses?
- Does the omission of epirubicin from 3-drug therapy compromise treatment outcomes in this population (3 versus 2 drugs)?
- Does the omission of epirubicin and oxaliplatin compromise treatment outcomes in this population (3 versus 1 drugs)?

3.c Secondary trial questions:

- Does an objective health assessment tool applied at baseline help predict which patients will have favourable outcomes with chemotherapy?
- Does chemotherapy result in measurable changes in the health assessment scores?
- Is quality of life (QoL) improved by the trial treatments?

4 Outcome Measures (feasibility study)

Primary

1. The rate of patient randomisation into 321GO over the 18-month recruitment period in the 2 participating cancer networks.
2. The number of patients at each participating network considered for palliative chemotherapy for advanced GO cancer, and the proportion randomised into 321GO.

Secondary

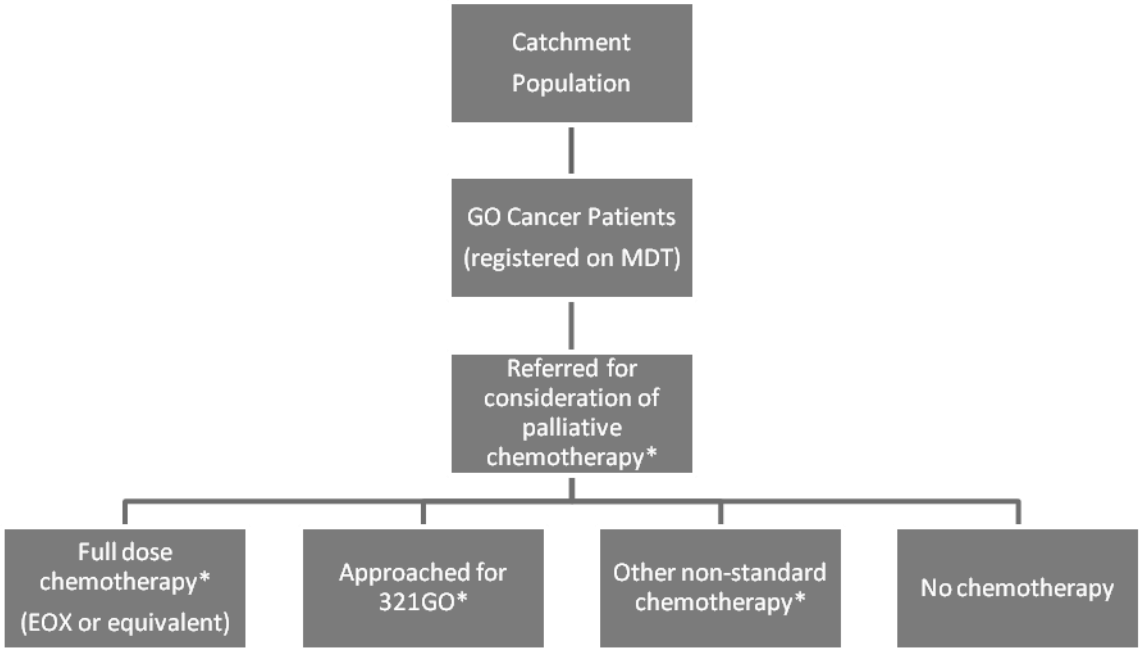
1. The tolerability of each regimen, assessed in terms of
    a. the incidence of CTCAEv3 grade ≥3 non-haematological toxicities at 6 weeks,
    b. the incidence of SAEs and dose delays/reductions, and
    c. the ability/willingness to dose-escalate to 100% at week 6.
2. Patient acceptability scores
3. Quality of life, nutritional and symptom changes
4. Progression-free survival for the whole group (combining all 3 treatment arms)

5 Centre Patient Selection and Registration

5.a Centre registration

- Registering centres must provide confirmation of local management (R&D) approval and a list of nominated trial personnel (via a copy of the site authorisation/delegation log). Confirmation of site REC SSA will be sent to the Chief Investigator from the main REC.

5.b Patient Registration



*All patients within these categories must be recorded on the trial "GO cancer referral log" in each recruiting centre.

We are recording this information to assess the feasibility of recruitment into a potential national phase III RCT. On the basis of expected recruitment numbers in the Yorkshire & Humber region, we would anticipate approximately 45 patients being enrolled into 321GO over the course of the 18-month recruitment period.

It is the responsibility of the PI to ensure data collection within the MDT and departmental record is complete. Please complete the GO cancer referral log for **ALL** patients referred for consideration for palliative chemotherapy who were **NOT** randomised into the trial. The GO

cancer referral log should be completed and sent in to the CTRU monthly during the recruitment phase of the trial. This is in place of a "non-randomisation log."

5.c Consent

- Where chemotherapy is an indicated treatment by the attending medical staff, a full verbal explanation of the trial and Patient Information Leaflet will be provided by either the attending medical staff (and/or the trial Clinical Research Nurse) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the study. Following information provision, patients will have as long as they need to consider participation, normally a minimum of 24 hours, and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial.
- Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. A record of the consent process detailing the date of consent and all those present will be kept in the patient notes. The formal assessment of eligibility and written consent will be taken by a clinician, who has signed/dated the staff authorisation/delegation log. The process of obtaining written consent will be clearly documented in the patient's medical notes
- The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. The original consent form will be retained in the investigator site file, a copy of the consent will be given to the patient, a second copy filed in the hospital notes (as per local practice) and a third copy will be returned to the University of Leeds CTRU.
- The responsibility for treatment with chemotherapy and the prescription of chemotherapy ultimately remains with the Principal Investigator (PI).
- The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

5.d Patient Selection

Eligibility Criteria

- Histologically confirmed carcinoma of the oesophagus, GO-junction or stomach, of either squamous, adenocarcinoma or undifferentiated type.
- With or without distant metastases, but if M_0, planned for treatment with palliative intent.
- No previous palliative chemotherapy for GO cancer
- Considered by the treating consultant to be fit/suitable for reduced-dose chemotherapy (normally WHO PS ≤2).
- Renal function: estimated GFR (eGFR) ≥30 ml/min
    - if eGFR is <30 ml/min, patient may still enter if measured EDTA/DTPA GFR is done and result is >30)
    - if eGFR (or measured GFR) is in range 30-50 ml/min, patient may enter 321GO but requires reduced doses (see Appendix V)
- Hepatic function: biliribin <3 times upper limit of normal (xULN) and transaminase (either AST or ALT) <5 xULN
    - if bilirubin is 1.5 - 3 xULN or AST/ALT is 2.5 - 5 xULN, patient may enter 321GO but requires reduced doses (see Appendix V)
- Bone marrow function: absolute neutrophil count (ANC) >1.5 $x10^9$/l; white blood cell count >3 $x10^9$/l; platelets >100 $x10^9$/l.
- Projected life expectancy of at least 3 months
- For women of child bearing potential, negative pregnancy test and adequate contraceptive precautions.

Exclusion Criteria

- Fit, suitable and willing for standard full-dose combination chemotherapy with EOX or equivalent.
- Medical or psychiatric condition impairing ability to consent or comply with assessments including QoL questionnaire.
- Other malignancy which, in the opinion of the treating consultant would potentially impede interpretation of the outcome of 321GO therapy.
- Treatment with another investigational agent within 30 days of commencing treatment.
- Current uncontrolled cardiac impairment.

- Medical condition requiring ongoing treatment with a contraindicated medication (sorivudine, brivudine, cimetidine)
- Patients previously treated with anthracyclines must not exceed total cumulative dose of epirubicin of 900mg/m^2 (or equivalent thereof, if a different anthracycline has been administered in the past) including the treatment to be administered within this trial.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Known hypersensitivity to epirubicin, oxaliplatin, capecitabine or fluoropyrimidines
- Age <18 years

Note: CT scan not required for eligibility but must be performed prior to treatment

6 Treatment of Patients

6.a Starting Chemotherapy

- Patients should start chemotherapy within 14 days of randomisation.
- The initial treatment plan is for 12 weeks of chemotherapy (4 cycles), with further treatment based on clinical benefit (see section 6.c below).
- Appendix I contains protocols for the three trial regimens. It is the responsibility of the treating consultant to ensure that these protocols are followed. In particular:
    - Renal, hepatic and bone marrow function must be monitored carefully, and dose-adjustments made as indicated (see appendix V).
    - Dose modifications should only be made after consulting the written protocols (if in doubt, please discuss with chief investigator).
    - Note that significantly obese patients have doses capped if Body Mass Index is greater than 30 (see appendix II).

6.b Discretionary dose increase at 6 weeks

- For each of the three regimens, the starting doses given in this protocol are 20% lower than the typical doses used in other recent or ongoing phase III trials. Patients should be reviewed by the responsible clinician at 6 weeks, when a dose increase from the initial 321GO doses up to full standard doses may be considered.

- Only patients who tolerate the first 6 weeks of treatment with no or minimal toxicity should be considered for dose increase:
    - do not dose-increase any patient who has experienced grade 3 haematological or grade 2 non-haematological toxicity at the starting dose level, or has required dose delay whether for toxicity or inter-current illness.
    - Patients considered unfit for dose increase at the 6-week review should not subsequently be dose-increased.
- Even in the absence of toxicity, dose increase is at the discretion of the treating consultant, not mandatory. It requires clinical review and discussion with the patient.
- A case record form will be completed at 6 weeks to record if the dose was increased or, if not, whether this was due to toxicity, patient choice or clinician choice. This contributes to the primary outcome measure of the study (see section 4).

6.c Chemotherapy duration and breaks

- The initial treatment period is 12 weeks (4 cycles)
- The patient should be scheduled for repeat CT scan during week 10 or 11, then a clinic visit (approx 12 weeks after initiating treatment) for review by the treating clinician. The LHA is also due at this time point.
- On the basis of the radiological and clinical review, the clinician should decide whether the outcome of treatment has been:
    - **"benefit":** (= No radiological progression, **and** no clinical deterioration). or
    - **"no benefit":** (= Radiological progression, **or** clinical deterioration).
- Patients with **benefit** should continue to a maximum of 8 cycles.
- Patients with **no benefit** may be considered for second-line therapy off trial.
- Treatment may be stopped at any time, at the discretion of the responsible consultant, if clear evidence of "no benefit" emerges between scheduled assessment points.

6.d Further chemotherapy after the 321GO plan

- When there is disease progression after first-line treatment within 321GO, options of further chemotherapy or purely symptomatic treatment may be considered.

6.e Other anticancer treatment modalities

- If, in the opinion of the treating consultant, an alternative treatment modality becomes indicated at any stage, it may be offered (e.g., palliative radiotherapy, surgery or oesophageal stent).
- If appropriate, 321GO trial treatment may be continued after the other treatment.

6.f Follow-up

- Once randomised, patients remain evaluable for the calculation of median progression-free survival (PFS) to inform the sample size calculation of the Phase III trial, regardless of their subsequent course and treatment. Follow-up data on all patients, including details of other treatments given, is therefore important and will be collected up to 1 year post randomisation.
- Patients enrolled from the UK will be registered with the NHS Information Centre Medical Research Information Service in order to obtain long term follow-up information on survival, in the event that patients are lost to follow-up in the clinical centres.

6.g End of Trial

- The end of the trial is defined as the date of the last patient's last treatment visit plus 30 days. Short-term follow-up to 48 weeks post-randomisation constitutes the non-intervention phase of the trial.

7 Trial drugs

7.a Drug supplies

- All drugs and other products used in this trial are commercially available. No special trial stock is available. In the event of a safety issue or Investigational Medicinal Product quality issue mechanisms to enable tracing back to a particular trial participant will be in place. These are detailed in the 321GO Pharmacy and Investigational Medicinal Product Standard Operating Procedure.
- Off-the-shelf supplies of epirubicin, oxaliplatin and capecitabine will be used and labels will be provided for use at the time of dispensing; all are classed as IMPs within this trial. The drug batch number will be added to a trial specific prescription and/or recorded on the accountability logs.
- The guidelines in this protocol are in line with manufacturers' recommendations at the time of writing, but Summaries of Product Characteristics (SPCs) are updated from time to time. Up-to-date SPCs are posted on the Electronic Medicines Compendium website (http://emc.medicines.org.uk/).

7.b Prescribing and compliance

- Chemotherapy prescriptions should conform to local best practice including computerised prescribing systems.
- Capecitabine prescriptions to take home should include exactly the correct number of tablets for the current cycle.
    - All capecitabine prescriptions must be accompanied by the diary sheet, completed by the pharmacist or research nurse, with instructions of how many tablets of each strength to take at each dose.
    - Ask the patient to return any unused tablets with the completed diary sheet, at the next visit.
    - Non-compliance is reported on the CRF at 6 and 12 weeks.
- The body surface area (BSA) should be determined using the preferred local method based on baseline weight and height. The BSA does not need to be recalculated unless there is a change in weight of more than 10% compared to baseline.

7.c Concomitant Medications

- **Brivudine** or **sorivudine** may produce a dangerous interaction with capecitabine. These medications are not licensed in the UK but may be prescribed for viral infections in other countries. Patients on these medications are excluded from participation in the trial.
- The following medications may interact with 321GO medications. These medications are not contraindicated but should be avoided unless there no reasonable alternative:
    - **warfarin**: no interaction with oxaliplatin, but INR control may be affected by capecitabine. More frequent INR monitoring is required if the patient is to continue warfarin.
    - **phenytoin:** blood phenytoin levels may increase with capecitabine.
    - **folic acid**: multivitamin supplements containing folic acid should be avoided as it could potentially increase capecitabine toxicity
    - **allopurinol**: may potentially reduce the effectiveness of capecitabine.

8 Trial procedures

	Baseline	Each cycle of chemo	If any SAE occurs	6 weeks (from start of chemo)	10-12 weeks	24 weeks	36 & 48 weeks
Clinical evaluation	X*	X			X	X	X
FBC, U&Es, LFTs	X*	X					
Nutritional Indices[$]	X[$]				X[$]	X[$]	
ECG, GFR[†]	X*						
NCI CTC scores		X					
WHO PS	X*	X			X	X	X
CT Scan (or equivalent)	X[¶]				X	X (if patient had not progressed at 12 weeks)	as clinically indicated
tumour marker (CEA and Ca 19-9 or alternative)	X[¶]			X (if raised at baseline)	X (if raised at baseline)	as clinically indicated	as clinically indicated
RECIST response + clinical benefit status					X	X	X
12 ml Blood Sample	X						
Pathology specimen sent to Leeds laboratory	X						
Questionnaires:**	CHA			TA	LHA	LHA	EQ-5D
Data to be returned to TRIAL CENTRE	CHA; Randomisation & Pretreatment form	Enter data on Treatment Form (return to CTRU 3-weekly)	SAE Report Form (Guidelines in section 9 in protocol)	6-Week Early Assessment Form; Chemotherapy Side Effects Questionnaire (in patient diary card)	LHA; 3-Month Progress Report Form	LHA; 6-Month Progress Report Form	EQ-5D; Follow-up Progress Report Form

** within 2 week prior to randomisation*
¶ within 5 weeks prior to starting chemotherapy
† measured GFR not required for randomisation if Cockcroft estimate Creatinine Clearance >30 ml/min
$ pre-albumin and transferrin
***please complete prior clinician review as this provides a more objective assessment and aids compliance*

8.a Within the week prior to randomisation:

- **Complete baseline procedures:**
  - history and examination
  - assessment of performance status
  - full blood count and biochemistry . Calculate GFR using Cockroft formula (see Appendix IV). If the Cockroft estimate is < 50 ml/min, a measured GFR is required (e.g. by EDTA clearance). (The measured GFR is not required prior to randomisation or the commencement of chemotherapy but should be arranged prior to the second cycle.)

- ensure that a baseline CT scan has been (or will be) performed **within 5 weeks prior to the planned start date for chemotherapy**
- check all other inclusion and exclusion criteria in protocol section 5.d

- **Then obtain the patient's written consent**

- **After obtaining written consent but prior to Randomisation:**
  - Perform **Comprehensive Health Assessment (CHA).** NB this will take 30-60 mins so may require a separate visit.

8.b Randomisation:

- Participating centres will randomise patients using the randomisation system based at the CTRU within working hours (Monday – Friday, 9am-5pm excluding Christmas, Easter and bank holidays). Access will only be granted to centres which are fully approved and from which all the necessary documentation has been received.
- Randomisation will only proceed if eligibility criteria have been checked, written consent obtained and the baseline CHA has been completed.
- Patients will be randomised on a 1:1:1 basis to receive either EOX, OX or X treatment and will be allocated a trial number. Stratified permuted block randomisation will be used to ensure treatment groups are well-balanced for the following patient characteristics, details of which will be required for randomisation:
  - Age (≤75 years vs. >75 years)
  - Presence of distant metastases (yes vs. no)
- To randomise a patient, complete the first page of the Randomisation Form and telephone the CTRU:

Direct line for randomisation: 0113 343 4930
Monday – Friday, 9 a.m. – 5 p.m.

This section details the procedures for retrieval of pathological material and blood samples for those patients who have consented to these optional additional bits of research

- **If the patient has consented for the retrieval of pathology material, please:**

- Request patient's pathology specimens (both normal and tumour tissue), if available
- Ensure the pathologist completes the Pathology Details form
- Obtain the pathology report
- Anonymise the pathology report (blacking out all patient information) and write the patient's trial number, initials and date of birth on the report and the tumour block
- Send in to the Leeds laboratory at the address below
- Complete the appropriate section on the Pathology/Blood Sample CRF

- **If patient has consented for the blood sample, please**
  - Collect the 12 ml sample within 4 weeks of randomisation
  - Anonymise it with the patient's trial number
  - Send in to Leeds laboratory at the address below
  - Complete the appropriate section on the Pathology/Blood Sample CRF

- Send in the Pathology/Blood Sample CRF once all data is completed

Leeds Laboratory:

***321GO* Trial**
c/o Dr Susan Richman
Leeds Institute of Molecular Medicine
Section of Pathology and Tumour Biology
Wellcome Trust Brenner Building
St. James's University Hospital
Leeds LS9 7TF UK

8.d Start of chemotherapy:

- Treatment should start within 14 days of randomisation.
- Take blood for nutritional indices (pre-albumin and transferrin)
- Electrocardiogram

8.e Every chemotherapy cycle (Day 1, or up to 3 days before):

- Clinical evaluation (doctor/nurse), to include toxicity scores from previous cycle and current WHO PS
- Check FBC, U&Es, and LFTs.
- Record capecitabine compliance from previous cycle using tablet returns and patient diary
- These data should be collated on the **Treatment Form** which is returned to the CTRU after the administration of every cycle (i.e., every 3 weeks) and after the last cycle.

8.f Six weeks after starting chemotherapy (before cycle 3):

- Schedule clinic appointment with consultant to assess progress
- Re-check tumour marker (CEA and/or CA19.9) if raised at baseline
- Consideration of dose increase is made at this appointment (see section 6.b)
- This decision is recorded and returned to the CTRU using the **6-Week Early Assessment Form**
- **Chemotherapy Side Effects Questionnaire** is completed by the patient in the Patient Diary for cycles 1 and 2. This questionnaire is only done **once** and should be returned to the CTRU after cycle 2 has been completed.

8.g Three months after starting chemotherapy (wk 10-12)

- Schedule reassessment imaging (usually CT scan)
- Perform the Limited Health assessment (**LHA**):
  - This is a shortened version of the collection of QoL and general health assessment tools used in the CHA. It is administered by the research nurse or data manager (section 10.b)
- Complete the **3-Month Progress Report Form**. This includes:
  - treatment response (RECIST criteria, see Appendix VIII)
  - "treatment benefit" assessment
- Biochemical nutritional screen – pre-albumin, transferrin.

8.h Six months after starting chemotherapy

- Repeat the **LHA** at this visit
- Complete the **6-Month Progress Report Form**. This includes details of current response status and treatment
- CT scan if patient had not progressed at 3-month CT
- Biochemical nutritional screen – pre-albumin, transferrin.

8.i Three-monthly until one year post-randomisation

- Follow-up data are reported every 3 months until a year post-randomisation (e.g., follow ups should be done at 9 and 12 months), using the **Follow-up Progress Report Form**.
- No further detailed LHA data are required, but a short questionnaire (**EQ-5D**) is required to be completed by the patient, to give limited QoL data for health economic evaluation.
- When death occurs, this should be reported on the next **Follow-up Progress Form.** A **Death Form** should also be completed and reported to the CTRU within 7 days. If applicable, an SAE should also be reported to the CTRU. (see section 9.b.)

9 Pharmacovigilance

9.a Defining Adverse Events

- An adverse event (AE) is any untoward medical occurrence in a patient during or following administration of an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the trial drugs, whether or not considered related to the trial drugs.

9.b Defining Serious Adverse Events (SAEs)

- A Serious Adverse Event is defined in general as an untoward (unfavourable) event, which:
    - is fatal. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the last administration of the study agent must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such.
    - is life-threatening
    - requires or prolongs hospitalisation
    - results in persistent or significant disability or incapacity
    - is a congenital anomaly or a birth defect, or
    - may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above
    - Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the investigator requires reporting.

9.c Defining Suspected Unexpected Serious Adverse Reactions (SUSARs)

- All SAEs assigned by the local investigator as both suspected to be related to the trial drugs and unexpected are subject to expedited reporting. An event is unexpected when information is not consistent with the available product information or if they add significant information on the specificity or severity of an expected reaction

9.d Reporting AEs

- AEs will be collected for all patients and will be evaluated for duration and intensity according to the NCI Common Toxicity Criteria v.3.
- AEs will be collected for all patients from randomisation until 30 days after the last dose of treatment with a protocol IMP.
- Information about AEs, whether volunteered by the patient, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the CRF.
- A copy of all reported AEs will be sent to the sponsor if requested.

9.e Reporting SAEs

- SAEs will be collected for all patients from randomisation until 30 days after the last dose of treatment with a protocol IMP.
- All investigators should refer to the Summary of Product Characteristics (SPC) or Investigators Brochure when determining whether a SAE is expected.
- SAEs must be reported on the Trial SAE form and faxed to the CTRU on 0113 343 7985, within 24 hours of any member of the hospital research team becoming aware of the SAE.

9.f Reporting SUSARs

- All SAEs assigned by the local investigator as both suspected to be related to protocol-treatment and unexpected will be reviewed by the Chief Investigator (CI).
- Such SAEs will be classified as SUSARs and will be subject to expedited reporting to the REC and MHRA.
- All SUSARs occurring whilst on trial (until 30 days after the last dose of treatment with a protocol IMP) must be reported on the Trial SAE form and faxed through to the CTRU on 0113 343 7985, within 24 hours of any member of the research team becoming aware of the SUSAR.
- The CTRU will inform the MHRA,[1] the Main Research Ethics Committee (MREC)[2] and the Sponsor[3] of SUSARs within the required expedited reporting timescales.

[1] SUSARs must be reported to the REC / MHRA within 7 calendar days of the CI (or their research team) being informed of the event, if they result in Death or are deemed to be life-threatening. Follow-up information must be reported within 8 calendar days.

[2] Any SUSARs not resulting in Death or deemed to be life-threatening must be reported to the REC / MHRA within 15 Calendar days of the CI (or their research team) being informed of the event. Follow-up information must be reported within 8 calendar days.

[3] All SUSARs must be reported to the sponsor QA office (on 0113 – 39 26397) within 24 hours of the event being reported to the CI (or their research team).

9.g Annual Safety Report (ASR)

An ASR will be submitted to the main REC, MHRA and the Sponsor on the anniversary of the Clinical Trial Authorisation being granted; this will be prepared by the CTRU and CI.

The CI will review and sign / date the report.

10 General Health and QoL Assessments

10.a Choice of Instruments

- Analysis of the FOCUS2 data has been used to help determine for this trial which of the instruments may be of most use as outcome measures in the elderly and frail palliative chemotherapy population (see appendix XVI).
- The EORTC QLQ-C30, a modular QoL tool, will be used in the 321GO trial. However for the purposes of this trial, more detailed information is required on certain aspects of QoL than the QLQ-C30 modules provides. Therefore, questions from QLQ-C30's global and symptom modules are used, but specialist tools have been chosen to replace several modules:
  - Activities of Daily Living (ADL) will be examined using the 24-point Nottingham IADL tool.[27]
  - Satisfaction with treatment is addressed using additional questions previously used in MRC trials
- Physical fitness and co-morbidity: several components of physical fitness are being measured at baseline as they may contribute to "fitness for chemotherapy." We have replaced some of the mental health assessment, which proved less useful in FOCUS2, with a more detailed nutritional assessment.
  - Nutrition: a mini-nutritional assessment questionnaire (MNA)[28] and biochemical parameters (pre-albumin and transferrin).
  - Medical Co-Morbidity: the Charlson co-morbidity score is a validated tool for quantifying co-morbidity in the geriatric population.[29]
- EuroQol (EQ-5D) is a widely used generic measure of health status which, through a valuation survey of 3,500 members of the public provides a link to health state preferences. This provides a route for calculating Quality-Adjusted Life-Years (QALY) for cost-effectiveness analysis.
- We have designated the above collection of QoL and physical fitness tools the "**Comprehensive Health Assessment – CHA**". These assessments have been validated in the geriatric literature[30,31] and have been applied in European and American oncology units.[32,33]
- A shortened version of this assessment is used at the 12- and 24-week time points, designated the "**Limited Health Assessment – LHA**". This does not include the MMSE or Charlson co-morbidity score, so is quicker to administer.
- The 6 week patient reported toxicity assessment will be applied as a separate assessment.

10.b Administration of the CHA and LHA tools

- The CHA and LHA are administered in the outpatient clinic by the research nurse. CHA takes approximately 40 min and LHA approximately 20 min to administer.
    - One person in each centre must be nominated to take responsibility for the administration, collection, checking and sending off of the QoL forms.
    - Both CHA and LHA consist of a nurse-administered section and a patient-completed questionnaire.
    - The patient-completed questionnaire should be completed by the patient in the clinic prior to clinician review as this aids objectivity and compliance. The research nurse or data manager should be available to assist (e.g. with reading questions or marking responses) if the patient requires. This person should also check through the questionnaire after completion and ensure that all questions have been answered, and that the patient ID and date are completed.
    - **All questionnaires should be returned to the CTRU after completion.**
- The baseline (CHA) assessment may be performed at the same visit as consent and randomisation, and must be within 4 weeks prior to starting chemotherapy.
- A window of 3 weeks each side of target follow-up LHA is acceptable.
- Please note that, once randomised, all patients remain in the trial and the follow-up LHA data are required even if patients do not complete protocol treatment.

11 Molecular pathological research

Recent work has demonstrated the capacity for tumour molecular variables to be used to predict benefit from chemotherapy ("chemoprediction"). There may also be potential to predict either tumour response or excessive drug toxicity by examining normal tissue DNA for genetic polymorphisms in key enzymes in drug metabolic pathways ("pharmacogenetics").

- Consenting patients' stored pathological samples are sent to the Leeds laboratory at the time of trial registration. Samples will be analysed and held here.
- Up to four samples should be sent where available representing:
    - Primary tumour
    - Normal mucosa of the upper gastrointestinal tract
    - Lymph node metastasis
    - Distant metastasis
- The research nurse should anonymise the samples with the patient's trial number, initials and date of birth and send them to the processing laboratory in Leeds. (For further information, see Section 8.c). Sample preparation will include preparation of normal and tumour tissue microarrays (TMAs), RNA and DNA extraction.
- An anonymised 12ml blood sample will also be sent to Leeds for preparation of DNA for SNP analysis.
- The samples will be considered the property of the sponsor of the trial. Proposals for translational research projects involving the material will be considered by the TMG.

12 Analysis plan and statistics

As this is a feasibility study, data will be summarised using descriptive summary statistics only i.e. no statistical testing will be carried out.

12.a Primary Analysis: Feasibility

The primary purpose of this study is to assess the feasibility of a phase III national trial with the same patient selection criteria and design.

We anticipate that PFS in the frail/elderly GO cancer patients will be approximately 2/3rds that of the usual trial population, i.e. around 4.6 months (based on PFS of 7 months in REAL2). However, this figure may be amended based on 321GO data. The phase III trial is planned as a non-inferiority trial, using a non-inferiority margin of 1 month reduction in median PFS. Using these figures we will need 238 patients per arm with 80% power and a 1-sided 5% significance level (based on a 1-sided log-rank test assuming patients are followed for a fixed length of time and that the hazard ratio is constant). We will be looking at non-inferiority (with the same margin of non-inferiority) of both OX and X compared to EOX i.e. two separate comparisons, and therefore will need to recruit ~720 patients in total giving 408 events for each comparison.

The Yorkshire and Humber Networks have a combined population of 3.5M, representing 5.7% of the UK population. To translate accrual figures in the feasibility study to potential national recruitment in a phase Ill trial, two approaches will be used:

I. Population-based. We will assume that because of local interest and "ownership", recruitment in a national trial would be at only half the rate achieved in our networks. On this basis, accrual of over 45 patients in 18 months in the feasibility study would suggest that a national trial could exceed 250/yr (0.5 x 30 x [100/5.7]), or 750 over 3 years. This would give confidence to propose a phase Ill trial with PFS as the primary endpoint. Recruitment of 30-45 patients would suggest that a smaller-scale national trial is feasible, with 450-700 patients, and consideration would be given to the choice of primary endpoint, including QoL (as used in FOCUS2). Accrual of fewer than 30 patients in the feasibility study would suggest that a national trial would struggle to recruit 500 patients in 3 years; this would therefore be our lower threshold. A sample size of at least 30 patients will also provide a reasonable estimate of PFS for our phase III sample size calculation.[34]

II. In relation to REAL-3. The centres participating in 321GO will also be recruiting their fitter/younger patients into REAL3. We will assess the relative rates of monthly recruitment to

the two trials at each centre. This will allow us to estimate the potential national accrual based on current actual rates of accrual to REAL3 at the time of completion of the feasibility study, to supplement the estimates in (I).

The number of patients who are referred for consideration of palliative chemotherapy for advanced GO cancer and those treated with full dose chemotherapy (EOX or equivalent), those approached for 321GO (but not randomised) and those receiving other non-standard chemotherapy, in addition to those randomised into 321GO, will also be summarised.

12.b Secondary Analyses: Tolerability/safety/acceptability

Tolerability of each regimen will be summarised descriptively. For the safety outcome tabulations, patients will be grouped according to the treatment they actually received, i.e., patients will only be included in the summary tables if they have received at least one dose of study treatment. Key measures of tolerability are:

- Rates of grade ≥3 haematological or non-haematological toxicity during the first 6 weeks (at the starting dose)
- Rates of SAEs
- Rates of dose delay, reductions or stop
- Rates of dose-escalation at the 6-week assessment point

Assessment will primarily be based on the first 6 weeks, i.e., the period spent at 80% standard doses, before planned escalation. Full tolerability data will continue to be collected for the duration of chemotherapy. For a regimen to be used in the phase III trial, an overall tolerability rate of >67% during this 6-week period is needed (i.e., <33% patients requiring dose-reduction/stoppage/delay or experiencing grade ≥3 toxicity).

12.c Secondary Analyses: PFS estimate

The overall median PFS estimate and its corresponding 95% confidence interval (CI) will be calculated to inform the sample size calculation of the Phase III trial. As this is to aid the design of a pragmatic Phase III trial, all randomised patients will be included in the calculation, regardless of whether or not they have received study treatment. PFS is defined as the time from the date of randomisation to the date of disease progression or death from any cause. Patients with missing follow-up data, or who are alive and progression free at the time of analysis, will be censored at the last date they were known to be alive and progression-free (date of last disease assessment). Disease progression is defined as either clinical or radiological evidence of disease progression. Where both a clinical exam and a scan have been carried out, the date of the clinical exam will be used as the date of disease progression.

12.d Secondary Analyses: Quality of life, nutritional and symptom data

The number of patients who complete the QoL questionnaires at each follow-up time-point and the number of missing items on each questionnaire will be summarised.

If it is determined that QoL will be the primary endpoint for the Phase III trial, QoL data will be summarised using adjusted for baseline mean scores and 95% CIs obtained from a multi-level repeated measures model where appropriate. Data will also be summarised descriptively using bar charts, box plots, and summary tables. Again, to aid the design of a pragmatic Phase III trial, all randomised patients will be included in the summaries, regardless of whether or not they have received study treatment

12.e Secondary Analyses: Data monitoring

Given that this is a feasibility study, not a Phase II trial, and uses standard agents at reduced doses, no formal interim analyses with fixed stopping rules are planned. However an independent Data Monitoring and Ethics Committee (DMEC) will be established to review the safety and ethics of the trial and to make appropriate recommendations if unexpected rates of toxicity are noted. Detailed unblinded reports will be prepared and presented to the DMEC in strict confidence at 6-monthly intervals.

13 Trial Management

This trial is being undertaken in accordance with the Principles of GCP. All personnel involved in the trial should hold an up to date GCP training certificate. Responsibilities of the trial personnel and committees are as follows:

The **Chief Investigator** (CI) and the trial management group are responsible for the day-to-day running of the trial. The **Trial Management Group** (TMG) is based at the St James Institute of Oncology and will be supported by the University of Leeds Clinical Trials Research Unit (CTRU) which will be responsible for Randomisation, Data Management, Pharmacovigilance, Site Monitoring and Statistical Analysis. There will be a named PI at each of the non-central recruiting centres within the Yorkshire Cancer Research Network.

The approved trial protocol master copy is held by the Trial Management Group (TMG). Each recruiting centre will have local measures to ensure the current protocol version replaces all other copies where amendments to the protocol are made.

14 Publication

The results from all centres will be summarised together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the study until the TMG has published its report. The TMG will form the basis of the Writing Committee and will advise on the nature of publications.

All publications shall include a list of investigators at each centre, and if there are named authors, these should include the PI(s), Clinical Co-Investigator(s), Clinical Trial Manager(s), and Statistician(s) involved in the trial. If there are no named authors, then a Writing Committee will be identified.

15 Data Collection, Source Data and Confidentiality

Patient confidentiality will be respected at all times throughout this trial. The name of a patient will be collected at randomisation as this will be required for flagging purposes. However, on all subsequent forms and on any correspondence the patient's trial number, initials and date of birth will be used.

15.a General

All information collected during the course of the trial will be kept strictly confidential.

Information will be held securely on paper and electronically at the Clinical Trials Research Unit.

The participating centres will comply with all aspects of the Data Protection Act 1998 and operationally this will include:

- consent from patients to record personal details including name, date of birth, postcode, NHS ID and hospital ID.
- appropriate storage, restricted access and disposal arrangements for patients' personal and clinical details
- consent from patients for access to their medical records by responsible individuals from the research staff, the sponsor or from regulatory authorities, where it is relevant to trial participation
- consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.
- patients will not be named in any publications.
- a copy of the consent form will be sent to the CTRU.

15.b Archiving

In line with the principles of GCP/UK Clinical Trial Regulations guidelines, at the end of the trial, data will be securely archived at each participating centre for a minimum of 15 years. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will not be used in the trial analyses. No trial records may be destroyed without first obtaining written permission from the Sponsor.

Study documentation/data must not be destroyed without the approval of the Sponsor.

16 Regulatory and Ethics Approval

Appropriate ethical, regulatory and sponsor approval will be sought on confirmation of funding and prior to the first trial subject being consented into the study.

This clinical trial, which involves the use of investigational medicinal products has been designed and will be run in accordance with the Principles of GCP and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004 / 1031) and any subsequent amendments of the clinical trial regulations.

The trial will be performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa, October 2000. Informed written consent will be obtained from the patients prior to randomisation/registration into the study.

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. It cannot however provide insurance cover for claims arising from non-negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

17 Quality Assurance

The Sponsor has systems in place to ensure that there is reporting and appropriate action taken in respect of:

(a) serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation.

(b) urgent safety measures

(c) protocol violations

The Sponsor reserves the right to audit any site involved in the trial and authorisation for this is given via the RSA.

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

Investigators will promptly notify the Sponsor Quality Assurance (QA) Office of the following within the required timeframe, once they become aware of:

(a) serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation.

(b) urgent safety measures

(c) protocol violations

(d) any amendments to the trial

(e) any changes the Clinical Trial Risk Assessment (Form A)

(f) any other issues as stated in the Research Sponsorship Agreement (RSA)

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Appendix I – The chemotherapy regimens

The 321GO EOX regimen

Day 1 of treatment schedule (21-day cycle)

1) IV dexamethasone 8 mg + granisetron 1-3 mg or equivalent
2) epirubicin 40 mg/m^2 IV bolus
3) oxaliplatin 104 mg/m^2 IV infusion in 500ml 5% Glucose over 2 hours

Day 1 to 21

Capecitabine 500mg/m^2 bd for 21 days

Notes:

- Because of a potential in vitro chemical reaction between oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip tubing etc.
- Oral antiemetics from day 2: dexamethasone 4 mg tds x 1 day; 4 mg bd x 1 day; 4 mg od x 1 day. Domperidone or metoclopramide prn.
- For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc.), the oral steroid should be omitted.
- The treatment cycle includes 42 capecitabine doses taken 12-hourly. This starts with the evening dose on day 1 and ends with the morning dose on day 22
- Oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion.
- The capecitabine dose is rounded to the nearest achievable dose using the table in appendix II. The same dose is taken morning and evening.
- Patients are instructed to take capecitabine within 30 minutes after food, approximately 12 hourly (e.g. 8am and 8pm)
- In the unlikely event of the patient having had a limb previously amputated contact Chief Investigator for advice on dosing.

Dose escalation to full-dose EOX

Schedule the patient for review by the treating consultant 6 weeks after starting treatment (start of cycle 3). A dose increase to full dose may be considered at that point. See section 6.b for criteria for dose increase, but note especially that it is at the discretion of the treating consultant, not automatic

Full dose EOX regimen: as above except:

1. Epirubicin 50mg/m^2 IV bolus
2. Oxaliplatin 130 mg/m^2 IV infusion over 2 hours
3. Capecitabine 625 mg/m^2 bd 21 days

Scheduled tests

- FBC and clinical assessment (CTCAE toxicity scores) should be performed on the day of starting each cycle, or within 3 days before, and the results available before starting.
- Biochemistry (including creatinine, bilirubin, and either AST or ALT) is done at the same time as FBC; these results should either be available before starting the cycle or, if not, should be reviewed within 24 hours after starting the cycle (so that capecitabine can be interrupted if dictated by an elevated transaminase).

Toxicity and dose adjustments for EOX

Haematological

Dose Modifications as defined by FBC on day 1 of each cycle of treatment:

Neutrophils x10^9/L		**Platelets x10^9/L**	
>1.0	and	>75	FULL DOSE
0.5-0.9	or	50-74	Stop capecitabine and delay oxaliplatin and epirubicin until recovery. Restart capecitabine at full dose and reduce epirubicin dose by **25%** and oxaliplatin dose by **20%** on subsequent cycles.
<0.5	or	25-49	Stop capecitabine and delay oxaliplatin and epirubicin until recovery. Restart capecitabine at full dose and reduce epirubicin dose by **50%** and oxaliplatin dose by **20%** on subsequent cycles.
		<25	Stop capecitabine and delay oxaliplatin and epirubicin until recovery. Restart capecitabine at full dose and reduce oxaliplatin by **20%** on subsequent cycles. **Omit** epirubicin from subsequent cycles

- Grade 3 neutropaenia at any time on treatment requires a subsequent 25% dose reduction in epirubicin. Grade 4 neutropaenia or neutropaenic infection/fever at any time on treatment requires a 50% reduction in epirubicin.
- If a further delay(s) for myelotoxicity occurs despite a dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.
- GCSF may be used as per local guidance.

Non-haematological toxicities (excluding neurotoxicity – see below)

- Grade 1 toxicity is managed symptomatically and does not usually require dose reduction or interruption
- For any toxicity of grade 2 or higher (e.g. diarrhoea, mucositis, vomiting) **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.

- Note that when capecitabine is stopped for toxicity the **doses are omitted, not delayed**. If resolution to grade 0 – 1 occurs capecitabine is resumed for the remainder of the planned cycle.

- When resuming EOX after a pause for toxicity, use the following dose reduction scheme:
  - Grade 2 toxicity: resume at the same dose after first pause, but reduce all 3 drugs to 75% of the previous doses if a second pause is required.
  - Grade 3 toxicity: resume at 75% of original doses (all 3 drugs)
  - Grade 4 toxicity: discontinue permanently.
- If further toxicity of grade ≥2 occurs after a dose-reduction, the doses should either be reduced to 50% of the original dose, or stopped permanently, at the consultant's discretion.

Neurotoxicity (see appendix XVI)

- Oxaliplatin commonly causes peripheral sensory symptoms, easily distinguishable from capecitabine neurotoxicity, which is uncommon, and cerebellar.
- Many patients experience transient paraesthesia of hands and feet, or mild throat dysaesthesia, precipitated by cold and lasting several days after each oxaliplatin administration. They do not require treatment or dose reduction.
- If symptoms persist for 21 days (i.e. until the next cycle is due), and are associated with significant discomfort or loss of function (e.g. dropping objects), omit oxaliplatin and continue with epirubicin and capecitabine alone until fully recovered, then consider restarting EOX.

Renal function (see also Appendix V)

- Before starting, ensure patient fulfils eligibility for renal function. If Cockroft estimate GFR <50 ml/min, check GFR with EDTA clearance or equivalent. In the event that a Cockroft estimate is < 50 ml/min, a measured GFR is not required prior to randomisation or the commencement of chemotherapy but should be arranged prior to the second cycle. If GFR is in the range 30-49 ml/min, a 25% reduction in the dose of capecitabine is required (see appendix V). For purposes of dose escalation to 'full dose' at 6 weeks, 'full dose' is 75% of the standard dose in this situation.

Hepatobiliary function

- If bilirubin rises to 1.5 – 3 times the upper limit of normal during treatment epirubicin should be reduced by 50%. If bilirubin rises above 3 x upper limit of normal discuss with consultant as stopping chemotherapy may be indicated; refer to table in Appendix V.

Stomatitis

- Routine mouth care (e.g. Corsadyl, nystatin) is recommended.
- If mouth ulcers occur despite this, stop the capecitabine. Restart the capecitabine when they have resolved but reduce the capecitabine by 25% and continue at the lower dose for subsequent cycles.
- If further grade ≥2 stomatitis occurs, the doses should either be stopped permanently or reduced to 50% of the original dose at the treating consultant's discretion.

Diarrhoea

- For grade 1 diarrhoea occurring between cycles, treat symptomatically initially: loperamide 2-4 mg qds. and/or codeine phosphate 30-60 mg qds. as required.
- For diarrhoea of grade ≥2 **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.
    - Note that when capecitabine is stopped for diarrhoea the **doses are omitted, not delayed**. If resolution to grade 0 – 1 occurs before day 21, capecitabine is resumed for the remainder of the planned cycle; otherwise wait until the next cycle.
- When resuming capecitabine after a pause for diarrhoea, use the following dose reduction scheme:
    - Grade 2 toxicity: resume at the same dose after first pause, but reduce to 75% of the previous dose if a second pause is required.
    - Grade 3 toxicity: resume at 75% of original dose
    - Grade 4 toxicity: discontinue permanently.
- If further toxicity of grade ≥2 occurs after a dose-reduction, the dose should either be reduced to 50% of the original dose, or stopped permanently, at the consultant's discretion.

Hand-foot syndrome (HFS)

- Treat symptomatically, initially with pyridoxine 50 mg tds by mouth. Topical corticosteroid may also help.
- If HFS is still a problem, reduce the capecitabine dose by 25% for subsequent cycles.

DPD deficiency

- With any 5FU regimen, the occasional patient is encountered (approx 1-3%) who has markedly exaggerated toxicity due to reduced 5FU catabolism. If this occurs, await full recovery. Further treatment at much reduced 5FU dose (e.g. 50%) may be considered. Please discuss with one of the clinical coordinators.

Cardiotoxicity

- 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continued treatment with upgraded antianginal medication and reduced 5FU dose may be considered, alternatively consider non-5FU treatment off trial.
- Any patient who develops unexplained cardiac failure while on treatment should undergo evaluation of cardiac function with a MUGA scan or echocardiogram. If left ventricular is less than the lower limit of normal range then epirubicin should be omitted.

Allergic reactions to oxaliplatin

- Patients may develop acute hypersensitivity to oxaliplatin, usually only after several doses. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity, although full-blown anaphylaxis is rare

- If self-limiting hypersensitivity occurs, discontinue the infusion and treat with IV corticosteroid and antihistamine. The oxaliplatin infusion can be restarted on recovery, given over 6 hrs. If hypersensitivity occurs again, the oxaliplatin should be permanently discontinued.
- After full recovery, the patient may continue with epirubicin and capecitabine alone

Respiratory

- As with other platinum drugs, rare cases of acute interstitial lung disease or lung fibrosis have been reported with oxaliplatin. In the case of unexplained respiratory symptoms or signs, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

The 321GO X regimen

Treatment schedule (21-day cycle)

day 1-15: Capecitabine 1000 mg/m^2 bd (14 days)

day 16-21: no treatment

Notes:

- The full treatment cycle consists of 28 doses taken 12-hourly. This starts with the evening dose on day 1 and ends with the morning dose on day 15.
- The dose is rounded to the nearest achievable dose using the table in Appendix II. The same dose is taken morning and evening.
- Patients are instructed to take capecitabine within 30 minutes after food, approximately 12-hourly (e.g. 8 a.m. and 8 p.m.)
- In the unlikely event of the patient having had a limb previously amputated contact chief investigator for advice on dosing.

Antiemetics, etc:

- Patients should be prescribed a prn oral antiemetic (e.g. metoclopramide 10 mg tds)

Dose escalation to full-dose X

Schedule the patient for review by the treating consultant 6 weeks after starting treatment (start of cycle 3). A dose increase to full dose may be considered at that point. See 6.b for criteria for dose increase, but note especially that it is at the discretion of the treating consultant, not automatic

Full dose X regimen:

day 1-15: Capecitabine 1250 mg/m^2 bd (14 days)

day 16-21: no treatment

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle, or within 3 days before, and the results available before starting.
- Biochemistry (including creatinine, bilirubin, and either AST or ALT) is done at the same time as FBC; these results should either be available before starting the cycle or, if not, should be reviewed within 24 hours after starting the cycle (so that capecitabine can be interrupted if dictated by an elevated transaminase).

Toxicity and dose reductions/delays

Haematological

- Check FBC on (or the day before) day 1 of each cycle. Delay 1 week if, neutrophils < 1.0 x 10^9/l or platelets < 100 x 10^9/l. Only treat when neutrophils and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce capecitabine by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If a further delay(s) for myelotoxicity occurs despite a 20% reduction, a further dose reduction may be made, at the discretion of the treating clinician.
- GCSF may be used as per local guidance.

General Non-Haematological Toxicities

- NCI grade 1 toxicity is managed symptomatically and does not usually require dose reduction or interruption
- For any toxicity of grade 2 or higher (e.g. diarrhoea, mucositis, vomiting) **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.
    - Note that when capecitabine is stopped for toxicity the **doses are omitted, not delayed**. If resolution to grade 0 – 1 occurs before day 14, capecitabine is resumed for the remainder of the planned cycle; otherwise wait until the next cycle.
- When resuming capecitabine after a pause for toxicity, use the following dose reduction scheme:
    - Grade 2 toxicity: resume at the same dose after first pause, but reduce to 75% of the previous dose if a second pause is required.
    - Grade 3 toxicity: resume at 75% of original dose
    - Grade 4 toxicity: discontinue permanently.
- If further toxicity of grade ≥2 occurs after a dose-reduction, the dose should either be reduced to 50% of the original dose, or stopped permanently, at the consultant's discretion.

Renal function (see also appendix V)

- Before starting, ensure patient fulfils eligibility for renal function. If Cockroft estimate GFR <50 ml/min, check GFR with EDTA clearance or equivalent. In the event that a Cockroft estimate is < 50 ml/min, a measured GFR is not required prior to randomisation or the commencement of chemotherapy but should be arranged prior to the second cycle. If GFR is in the range 30-49 ml/min, a 25% reduction in the dose of capecitabine is required (see page 58). For purposes of dose escalation to 'full dose' at 6 weeks, 'full dose' is 75% of the standard dose in this situation.

Hepatobiliary function

- Capecitabine undergoes hepatic metabolism. In addition, patients on capecitabine may have temporary treatment-related elevation of transaminases; this requires interruption of treatment.

- If bilirubin rises above 1.5 x ULN during treatment, discuss with consultant as this may indicate disease progression. If treatment is to continue, refer to table in Appendix V.
- An isolated rise in transaminase above 2.5xULN during treatment is likely to be drug-related, and capecitabine should be interrupted until recovery and dose reductions may be required (see Appendix V).

The 321GO OX regimen

In view of a potential in vitro chemical reaction between oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip tubing etc.

Treatment schedule (21 day cycle)

day 1	IV bolus dexamethasone 8mg + granisetron 1-3mg or equivalent, then oxaliplatin 104 mg/m^2 IV infusion in 500 ml 5% glucose IV infusion over 2 hours
day 1-22	capecitabine 500 mg/m^2 twice daily

Notes:

- The treatment cycle includes 42 capecitabine doses taken 12-hourly. This starts with the evening dose on day 1 and ends with the morning dose on day 22
- Oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion.
- The capecitabine dose is rounded to the nearest achievable dose using the table on page 54. The same dose is taken morning and evening.
- Patients are instructed to take capecitabine within 30 minutes after food, approximately 12 hourly (e.g. 8 am and 8pm)
- In the unlikely event of the patient having had a limb previously amputated contact chief investigator for advice on dosing.

Oral antiemetics, etc:

- From day 2: dexamethasone 4 mg tds x1 day; 4 mg bd x1 day; 4 mg od x1 day.
- Domperidone or metoclopramide prn

Note on the use of dexamethasone

- For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted.

Dose escalation to full-dose OX

Schedule the patient for review by the treating consultant 6 weeks after starting treatment (start of cycle 3). A dose increase to full dose may be considered at that point. See section 6.b for criteria for dose increase, but note especially that it is at the discretion of the treating consultant, not automatic.

Full dose OX regimen, as above except:

day 1	oxaliplatin 130 mg/m^2 iv infusion over 2 hours
day 1-22	capecitabine 625 mg/m^2 twice daily 21 days (42 doses total)

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle, or within 3 days before, and the results available before starting.

- Biochemistry (including creatinine, bilirubin, and either AST or ALT) is done at the same time as FBC; these results should either be available before starting the cycle or, if not, should be reviewed within 24 hours after starting the cycle (so that capecitabine can be interrupted if dictated by an elevated transaminase).

Toxicity and dose reductions/delays

Haematological

- Check FBC on (or the day before) day 1 of each cycle. Delay 1 week if neutrophils < 1.0 x 10^9/l or platelets < 75 x 10^9/l. Only treat when neutrophils and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce the capecitabine and oxaliplatin doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If a further delay(s) for myelotoxicity occurs despite a 20% reduction, a further dose reduction may be made, at the discretion of the treating clinician.
- GCSF may be used as per local guidance.

Non-haematological toxicities (excluding neurotoxicity – see below)

- Grade 1 toxicity is managed symptomatically and does not usually require dose reduction or interruption
- For any toxicity of grade 2 or higher (e.g. diarrhoea, mucositis, vomiting) **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.
    - Note that when capecitabine is stopped for toxicity the **doses are omitted, not delayed**. If resolution to grade 0 – 1 occurs capecitabine is resumed for the remainder of the planned cycle.
- When resuming OX after a pause for toxicity, use the following dose reduction scheme:
    - Grade 2 toxicity: resume at the same dose after first pause, but reduce both drugs to 75% of the previous doses if a second pause is required.
    - Grade 3 toxicity: resume at 75% of original doses (both drugs)
    - Grade 4 toxicity: discontinue permanently.
- If further toxicity of grade ≥2 occurs after a dose-reduction, the doses should either be reduced to 50% of the original dose, or stopped permanently, at the consultant's discretion.

Neurotoxicity (see appendix XVI)

- Oxaliplatin commonly causes peripheral sensory symptoms.
- Many patients experience transient paraesthesia of hands and feet, or mild throat dysaesthesia, precipitated by cold and lasting several days after each oxaliplatin administration. This does not require treatment or dose reduction.
- If symptoms persist until the next cycle is due, and are associated with significant discomfort or loss of function (e.g. dropping objects), omit oxaliplatin and continue with capecitabine alone until fully recovered, then consider restarting OX

Renal function (see also appendix V)

- Before starting, ensure patient fulfils eligibility for renal function. If Cockcroft estimate GFR <50 ml/min, check GFR with EDTA clearance or equivalent. In the event that a Cockroft estimate is < 50 ml/min, a measured GFR is not required prior to randomisation or the commencement of chemotherapy but should be arranged prior to the second cycle. If GFR is in the range 30-49 ml/min, a 25% reduction in the dose capecitabine is required (appendix I). For purposes of dose escalation to 'full dose' at 6 weeks, 'full dose' is 75% of the standard dose in this situation.

Hepatobiliary function

- Capecitabine undergoes hepatic metabolism. In addition, patients on capecitabine may have temporary treatment-related elevation of transaminases which require interruption of treatment.
- If bilirubin rises above 1.5 x ULN during treatment, discuss with consultant as this may indicate disease progression. If treatment is to continue, refer to table in Appendix V.
- An isolated rise in transaminase above 2.5xULN during treatment is likely to be drug-related, and capecitabine should be interrupted until recovery and dose reductions may be required (see Appendix V).

Respiratory

- As with other platinum drugs, rare cases of acute interstitial lung disease or lung fibrosis have been reported with oxaliplatin. In the case of unexplained respiratory symptoms or signs, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

Allergic reactions to oxaliplatin

- Patients may develop acute hypersensitivity to oxaliplatin, usually only after several doses. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity, although full-blown anaphylaxis is rare.
- If self limiting hypersensitivity occurs, discontinue the infusion and treat with i.v. corticosteroid and antihistamine. The oxaliplatin infusion can be restarted on recovery, given over 6 hrs. If hypersensitivity reoccurs again, the oxaliplatin should be permanently discontinued.
- After full recovery, the patient may continue with X alone

Appendix II – Dose calculations and banding

Centres may either follow dose banding as per protocol or adopt local practice (provided this gives doses within 5% of the per protocol dose)

Dose Capping:

The dose capping method takes into account the Body Mass Index (BMI):

Patients with height	<=149 cm:	cap at SA 1.5 m2
Patients with height	150-159 cm:	cap at SA 1.7 m2
Patients with height	160-169 cm:	cap at SA 1.9 m2
Patients with height	170-179 cm:	cap at SA 2.1 m2
Patients with height	>=180 cm:	cap at SA 2.3 m2

Using these ranges means that:
- no patient with BMI <25 is capped
- all patients with BMI >35 are capped
- for patients in the middle of each height range the cap cuts in at BMI 30.

BMI = (kg/m^2) = weight in kilograms divided by (height in meters)^2

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Capecitabine dose banding

First calculate the patient's surface area accurately to 2 decimal places.

Calculate the exact (not rounded) target dose of capecitabine.

For example, a patient on OX requiring 500 mg/m2, who's SA is 1.59 m^2, has an exact target dose of 1.59 x 800 = 795 mg.

Use the table to find the rounded dose and the number of tablets per dose:

Exact Target Dose within range (mg)	Rounded Dose (mg)	Number of tablets per dose	
		500 mg +	150 mg
401 – 575	500	1	0
576 – 725	650	1	1
726 – 900	800	1	2
901 – 1075	1000	2	0
1076 – 1225	1150	2	1
1226 – 1400	1300	2	2
1401 – 1575	1500	3	0
1576 – 1725	1650	3	1
1726 – 1900	1800	3	2
1901 – 2075	2000	4	0
2076 – 2225	2150	4	1
2226 – 2400	2300	4	2
2401 – 2575	2500	5	0

Complete the patient's diary sheet for the cycle, including the patient's name, the numbers of each tablet to take (at the top) and the day and date of each dose due (in the table). Give the diary sheet to the patient together with their tablets.

Oxaliplatin dose banding

As for capecitabine, first calculate the patient's surface area accurately to 2 decimal places, then calculate the exact target dose.

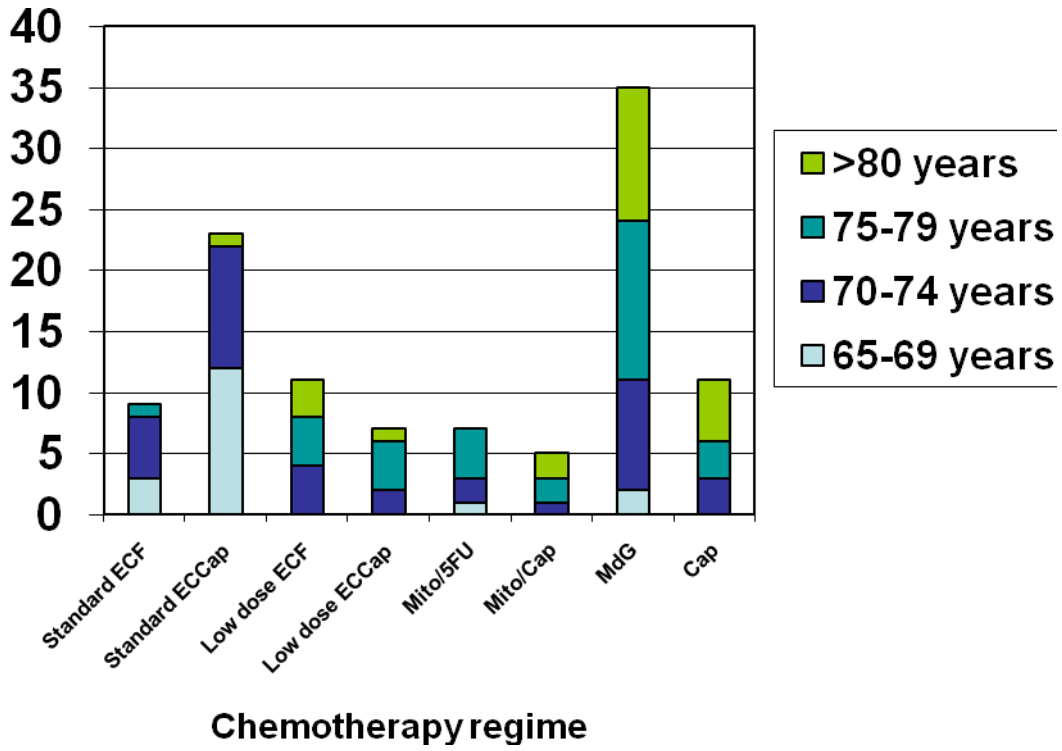
For example, the patient of 1.59m2 receiving the OX regimen without dose-adjustment would have a target dose of 104 x 1.59 = 165.36 mg

The oxaliplatin dose may be rounded to the nearest 10mg (or local practice may be followed) *So the patient in the above example would receive 170 mg oxaliplatin.*

Epirubicin dose banding – **not required – follow local practise**.

Appendix III – Current Practice in Leeds

Chemotherapy regimes used between 2002 and 2006 for the treatment of advanced gastroesophageal cancer in patients over the age of 65 years at Cookridge Hospital, Leeds, UK.



Appendix IV - Cockroft & Gault Formula

- The estimated GFR is given by:

  Males: $\frac{1.25 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}$

  Females: $\frac{1.05 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}$

- This formula usually under-estimates GFR by 10-30% compared with EDTA or measured 24-hour creatinine clearance, so is used in this trial as a screening test.
  - A Cockroft/Gault estimate of >50 ml/min is accepted as evidence of adequate renal function
  - Patients with a Cockcroft/Gault estimate of < 50 ml/min prior to randomisation should have formal GFR measurement with EDTA or 24 urinary creatinine.
  - In the event that a Cockroft estimate is < 50 ml/min, a measured GFR is not required prior to randomisation or the commencement of chemotherapy but should be arranged prior to the second cycle.
  - After the start of treatment, if the Cockroft/Gault estimate falls by >25% from baseline, to below 50 ml/min, the formal EDTA measurement should be re-checked.

Appendix V – Renal & hepatic function

		Epirubicin Dose	Oxaliplatin dose	Capecitabine dose
Renal function	GFR ≥ 50 ml/min	full	full	full
	GFR 30–49 ml/min	full	reduce by 25%	reduce by 25%
	GFR < 30 ml/min	off study - treat at discretion of responsible consultant		
Hepatic function	Bili ≤ 1.5 ULN and AST/ALT ≤2.5 x ULN	full	full	full
	Bili 1.5-3 x ULN and/or AST/ALT 2.5-5 x ULN	reduce by 50%	full	reduce by 50%
	Bili > 3x ULN or AST/ALT > 5 x ULN	off study - treat at discretion of responsible consultant		

Notes:

- Organ function at the time of enrolment must meet the eligibility criteria (see section 5).

- Note that patients with measured GFR in the range 30-49 ml/min may enter 321GO, but if randomised to receive capecitabine it is given at 25% reduced dose (as per table).

- If renal or hepatic function changes at any point after randomisation, use the table above. **Deteriorating organ function may be a sign of disease progression, so always discuss with the consultant oncologist.**
  - Use the more conservative guideline. E.g., for a patient with Bili <1.5x ULN ***and*** ALT > 2.5x ULN, reduce epirubicin.

- GFR: see notes in appendix IV for the use of Cockroft formula to estimate GFR. For patients with a Cockroft estimate <50 ml/min, a measured EDTA clearance (or 24 hour urinary creatinine clearance) should be obtained on at least one occasion, and this value takes precedence over the Cockroft estimate

- In the event that a Cockroft estimate is < 50 ml/min, a measured GFR is not required prior to randomisation or the commencement of chemotherapy but should be arranged prior to the second cycle.
- Dose reductions refer to a percentage of the indicated dose, for example in first cycle this will be a percentage of the starting doses which are already 80% of standard doses. In the event that doses are reduced due to impaired organ function and a dose escalation to standard doses is indicated at 6 weeks, organ-function specific reductions to the standard dose should be in place.

Appendix VI – Oxaliplatin Neurotoxicity Protocol

Toxicity	Duration of toxicity 1-7 days	Duration of toxicity >7 days	Persistent between cycles
Cold-related dysaesthesia	No reduction	No reduction.	Withhold oxaliplatin until recovery then restart with 25% reduction. Omit oxaliplatin if recurs.
Paraesthesia without pain	No reduction	No reduction	Withhold oxaliplatin until recovery then restart with 25% reduction. Omit oxaliplatin if recurs.
Paraesthesia with pain	No reduction	Reduce by 25% on subsequent cycles. Omit oxaliplatin if recurs.	Omit Oxaliplatin
Paraesthesia with functional impairment	No reduction	Reduce by 25% on subsequent cycles. Omit oxaliplatin if recurs.	Omit Oxaliplatin

Appendix VII – WHO performance status

Clinical Performance Status

0 Able to carry out all normal activity without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.

3 Capable only of limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Appendix VIII – RECIST response definitions

- RECIST (Response Evaluation Criteria In Solid Tumours) has now superseded the old WHO response criteria for solid tumours.
- The key differences are:
  - instead of measuring lesions in 2 dimensions it is now only necessary to measure the longest diameter.
  - disease is classified as measurable or not measurable but the term evaluable is no longer used

Measurable disease:

- Disease is measurable if there is at least one measurable target lesion. Target lesions should be selected on the basis of size and suitability for repeat measurement, up to a maximum of 5 measurable lesions per organ, and up to a maximum of 10 lesions in total. These should be representative of all involved organs.
- Target lesion must be accurately measurable in at least 1 dimension, with the longest diameter ≥20 mm (or ≥10 mm with spiral CT scan). If the lesion is smaller than this then it is classed as non-measurable.
- Measurements must be taken as close as possible to the beginning of treatment and never more than 4 weeks before the start of treatment. Target lesions should be assessed by CT, MRI or CXR, not by clinical assessment alone. The same imaging modality should be used throughout for any given patient.
  - When intra-venous contrast agents are given with CT, it is important to measure hepatic lesions in the same vascular phase on subsequent examinations
  - If MRI is used than the same sequence (e.g. T1 or T2 weighted images) in the same anatomical plane should be used.
- Add the longest diameters of the target lesions and report this as the **baseline sum longest diameter.** This will be used as a reference by which the tumour response will be measured.

Response definitions:

- **Complete response (CR)**: disappearance of all lesions (i.e. all evidence of disease, not just the target lesions) determined by 2 observations not less than 2 weeks apart (in 321Go the 12-week assessment should be used as the confirmatory assessment; there is no need for additional confirmatory scans.
- **Partial response (PR)**: ≥30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, with response or stable disease observed in non-target lesions, and no new lesions
- **Progressive disease (PD)**: ≥20% increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded, or unequivocal progression of non-target lesions, or appearance of new lesions.

Reminder:

- Response is judged against baseline, but progression is judged against the smallest recorded score.

Example:

Month	0	3	6	9	12
Measurement (mm)	100	90	50	55	65
Classification	baseline	SD	PR	PR	PD

References:

Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. J Natl Cancer Inst 2000, 92, 205-216
Gehan EA and Tefft MC. Will there be resistance to the RECIST (Response Evaluation Criteria in Solid Tumours)? J Natl Cancer Inst 2000, 92, 179-181

Appendix IX – NCI Common Toxicity Criteria (v3.0)

Toxicity	0	1	2	3	4	5
NAUSEA	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24hrs	Life-threatening consequences	Death
VOMITING	None	1 episode in 24 hours	2-5 episodes in 24 hours; IV fluids indicated < 24hrs	≥ 6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24hrs	Life-threatening consequences	Death
ANOREXIA	None	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition; IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALOPECIA	Normal	Thinning or patchy	Complete	-	-	-
HAND-FOOT SKIN REACTION	None	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, oedema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain, interfering with function	-	-
PAIN	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	-
STOMATITIS	None	Minimal discomfort, intervention not indicated	Symptomatic, medical intervention indicated but not interfering with ADL	Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
DIARRHOEA (patients without colostomy)	None	Increase of <4 stools/day over baseline	Increase of 4-6 stools/day over baseline; IV fluids indicated < 24hrs	Increase of ≥ 7 stools/day; incontinence; IV fluids ≥ 24hrs; hospitalisation	Life-threatening consequences (e.g., haemodynamic collapse)	Death
LETHARGY	None	Mild fatigue over baseline	Moderate or causing difficulty performing some activities	Severe fatigue interfering with ADL	Disabling	-
HAEMO-GLOBIN	Within normal limits	10.0g/dl - normal	8.0 - 9.9g/dl	6.5 - 7.9g/dl	<6.5g/dl	Death
PLATELETS	Within normal limits	$75x10^9/1$ - normal	50 - $74x10^9/1$	25 – $49x10^9/1$	<$25x10^9/1$	Death
WBC	Within normal limits	$3.0x10^9/1$- normal	2.0 - $2.9x10^9/1$	1.0 - $1.9x10^9/1$	<$1.0x10^9/1$	Death
NEUTROPHILS	Within normal limits	$1.5x10^9/l$ – normal	1.0 - $1.4x10^9/1$	0.5 - $0.9x10^9/1$	<$0.5x10^9/1$	Death
SENSORY NEUROPATHY	Normal	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
MOTOR NEUROPATHY	Normal	Asymptomatic; weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk indicated	Life-threatening; disabling (e.g., paralysis)	Death

These are selected categories. For full list see ***http://ctep.cancer.gov/reporting/ctc.html***

Appendix X - Summaries of Product Characteristics

Up-to-date copies of the Summary of Product Characteristics for epirubicin, oxaliplatin and capecitabine are available by following the web link:

http://emc.medicines.org.uk/

For consistency, SPCs produced by named manufacturers are identified as follows:

Capecitabine :	Roche Products Ltd
Oxaliplatin:	Sanofi – Aventis
Epirubicin:	Hospira UK Ltd

Appendix XI - List of Abbreviations

ADL – Activities of Daily Living

AE – Adverse Event

AIDS – Acquired Immune Deficiency Syndrome

ALL – Acute Lymphocytic Leukaemia

ALT – Alanine Aminotransferase

AML – Acute Myeloid Leukaemia

ASR – Annual Safety Report

AST – Aspartate Aminotransferase

Bili – Bilirubin

BMI – Body Mass Index

BSA – Body Surface Area

Ca19-9 – Carbohydrate Antigen 19-9

CC – Calf Circumference

CEA - Carcinoembryonic Antigen

CI – Chief Investigator

CHA – Comprehensive Health Assessment

CHF – Congestive Heart Failure

CLL – Chronic Lymphocytic Leukaemia

CML – Chronic Myeloid Leukaemia

CR – Complete Response

CRF – Clinical Research Form

CT – Computed Tomography

CTC – Common Toxicity Criteria

CTCAEv3 – Common Terminology Criteria for Adverse Events (version 3)

CTD – Connective Tissue Disease

CTRU – Clinical Trials Research Unit

CXR – Chest Xray

CVA – Cerebrovascular Accident

ECF – Epirubicin, cisplatin, fluorouracil

ECG – Electrocardiogram

EDTA – Ethylene Diamine Tetraacetic Acid

EOX – Epirubicin, Oxaliplatin, Capecitabine

EudraCT – European Clinical Trials Database

FBC – Full Blood Count

FU - Fluorouracil

GCP – Good Clinical Practice

GFR – Glomerular Filtration Rate

GO – Gastroesophageal

HFS – Hand-foot Syndrome

IADL – Instrumental Activities of Daily Living

IBW – Ideal Body Weight

IMP – Investigational Medicinal Product (European Union)

INR – International Nationalised Ratio

ISCTRN – International Standard Randomised Controlled Trial Number Register

IV – Intravenous

LFTs – Liver Function Tests

LHA – Limited Health Assessment

LREC – Local Research Ethics Committee

MDT – Multidisciplinary Team Meeting

MRC – Medical Research Council

NCI – National Cancer Institute

MAC – Mid-arm Circumference

MHRA – Medicines and Healthcare Products Regulatory Agency

MMSE – Mini Mental State Examination

MREC – Main Research Ethics Committee

MUGA – Multigated Acquisition

MRI – Magnetic Resonance Imaging

NCRI – National Cancer Research Institute

NHL – Non-Hodgkin's Lymphoma

ONS – Office of National Statistics

OS – Overall Survival

OX – Oxaliplatin, Capecitabine

PD – Progressive Disease

PFS – Progression Free Survival

PHT – Portal Hypertension

PI – Principal Investigator

PR – Partial Response

PS – Performance Status

PUD – Peptic Ulcer Disease

PV – Polycythaemia Vera

QA – Quality Assurance

QALY – Quality Adjusted Life Year

QoL – Quality of Life

RCT – Randomised Controlled Trial

REC – Research Ethics Committee

RSA – Research Sponsorship Agreement

RECIST – Response Evaluation Criteria in Solid Tumours

SA – Surface Area

SAE – Serious Adverse Event

SD – Stable Disease

SLE – Systemic Lupus Erythematosus

SPC – Summary of Product Characteristics

SUSAR – Suspected Unexpected Serious Adverse Reactions

TA – Toxicity Assessment

TIA – Transient Ischaemic Attack

TMG – Trial Management Group

TPN – Total Parenteral Nutrition

U&Es – Urea & Electrolytes

ULN – Upper Limit of Normal

WHO – World Health Organisation

X – Capecitabine