BALLAD UK

A TRIAL TO EVALUATE THE POTENTIAL BENEFIT OF ADJUVANT CHEMOTHERAPY FOR SMALL BOWEL ADENOCARCINOMA (IRCI-002)

THE UK COMPONENT OF THE GLOBAL BALLAD POOLED DATA ANALYSIS

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PROTOCOL APPROVAL SIGNATURE PAGE

This trial will be performed according to the Research Governance Framework for Health and Community Care (Second edition; 2006) and the Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2004:1031 (as amended) and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended)

Chief Investigator: Professor Jeff Evans

Signature:

Date (dd/mon/yyyy) **……**

Sponsor: Joanne McGarry

Signature:

Date (dd/mon/yyyy) **……**

Lead Statistician: Caroline Kelly

Signature:

Date (dd/mon/yyyy) **……**

Chief Investigator

Professor Jeff Evans
Professor of Translational Cancer Research /Consultant in Medical Oncology
University of Glasgow
The Beatson West of Scotland Cancer Centre
1053 Great Western Road
GLASGOW, G12 0YN
Tel: 0141 301 7116
Fax: 0141 330 7946
Email: j.evans@beatson.gla.ac.uk

International Lead

Professor Richard Wilson
Professor of Gastrointestinal Oncology
Wolfson Wohl Cancer Research Centre
Garscube Estate, Switchback Road
Glasgow
G61 1BD
Tel: 0141 330 3968
Fax: 0141 330 7196
Email:r.wilson@qub.ac.uk

Collaborator

Professor Rob McWilliams
Professor of Oncology
Mayo Clinic, Gonda 10 South
200 First Street, SW
Rochester, MN 55905, USA
Tel: 001-507-284-8432
Fax: 001-507-284-1803
Email: Mcwilliams.Robert@mayo.edu

Co-Investigator

Dr Kathleen A Boyd
Senior Lecturer Health Economics
R407
1 Lilybank gardens
Glasgow G12 8RZ
Tel: 0141 330 2713
Fax: 0141 330 5018
Email: Kathleen.Boyd@glasgow.ac.uk

Co-Investigator

Dr Janet Graham
Consultant in Medical Oncology
The Beatson WoSCC
1053 Great Western Road
Glasgow, G12 0YN
Tel: 0141 301 7147
Fax: 0141 330 7244
Email: janet.graham@ggc.scot.nhs.uk

Co-Investigator

Professor John Bridgewater
Professor in Medical Oncology
University College London Cancer Institute,
235 Euston Road
London, NW1 2BU
Tel: 020 3447 9093
Fax: 020 3447 9055
Email: j.bridgewater@ucl.ac.uk

Co-Investigator

Dr Kein Yim
Clinical Senior Lecturer
Institute of Cancer & Genetics
Cardiff University School of Medicine
Velindre Hospital
Cardiff, CF14 2TL
Tel: 029 2031 6206
Fax: 029 2019 6870
Email: Richard.Adams@wales.nhs.uk

Co-Investigator

Dr Naureen Starling
Consultant Medical Oncologist
Royal Marsden Hospital,
Fulham Road
London, SW3 6JJ
Tel: 020 8661 3158
Fax: 020 8643 9414
Email: naureen.starling@rmh.nhs.uk

Collaborator

Prof Thomas Aparicio
Department of Gastroenterology,
Avicenne Hospital,
AP-HP, Paris 13 University,
125 rue de Stalingrad,
93000 Bobigny, France.
Tel: +33 (0)148955434
Email: thomas.aparicio@avc.aphp.fr

Co-Investigator

Dr Mark Saunders
Consultant Oncologist
Christie Hospital
Wilmslow Road
Manchester, M20 4BX
Tel: 0161 446 3357
Email: Mark.Saunders@christie.nhs.uk

Co-Investigator
Professor Phil Quirke
Leeds Institute of Molecular Medicine,
University of Leeds,
Leeds, UK.
Tel: 0113 3438407
Email: P.Quirke@leeds.ac.uk

Collaborator
Professor dr. C.J.A. (Kees) Punt
Department of Medical Oncology, room F4-224,
Academic Medical Center, University of
Amsterdam, P.O.Box 22660
1100DD Amsterdam
The Netherlands
Tel: +31 20 5665955
Fax: +31 206919743
Email: c.punt@amc.uva.nl

Co-Investigator
Dr Jose Robles-Zurita Health Economist 1
Lilybank gardens
Glasgow G12 8RZ
Tel: 0141 330 5615
Email: JoseAntonio.Robles-Zurita@glasgow.ac.uk

Co-Investigator
Professor Manuel Salto-Tellez
Professor of Molecular Pathology
Centre for Cancer Research and Cell Biology
Queen's University Belfast
Belfast BT9 7BL, UK
Tel: 028 9097 2760
Email: m.salto-tellez@qub.ac.uk

Lead Statistician
Caroline Kelly Head of Biostatistics
Cancer Research UK Clinical Trials Unit
Level 0, Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow G12 0YN, UK
Tel: 0141 301 7188
Fax: 0141 301 7189
Email: Caroline.Kelly@glasgow.ac.uk

Project Manager
Sarah Bradley
Cancer Research UK Clinical Trials Unit
Level 0
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow G12 0YN, UK
Tel: 0141 301 7540
Fax: 0141 301 7946
Email: Sarah.Bradley@glasgow.ac.uk

Statistician
Elaine McCartney
Cancer Research UK Clinical Trials Unit
Level 0, Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow G12 0YN, UK
Tel: 0141 301 7198
Fax: 0141 301 7192
Email: elaine.mccartney@glasgow.ac.uk

Sponsor Representative
Joanne McGarry
Sponsor Research Co-ordinator
NHS Greater Glasgow and Clyde
Dykeybar Hospital
Grahamston Road
Paisley
PA2 7DE
Tel: 0141 314 4001
Email: mcgarjo410@ggc.scot.nhs.uk

Co-Sponsor Contact
Debra Stuart
Reserach Governance Manager
University of Glasgow
College of MVLS
Wolfson Medical School Building
Glasgow
G12 8QQ
Tel: 0141 330 4539
Email: debra.stuart@glasgow.ac.uk

Sponsor Pharmacist
Paula Morrison
NHS Greater Glasgow and Clyde Research & Development
Dykebar Hospital
Grahamston Road
Paisley
PA2 7DE
Tel: 0141 314 4019
Email: paula.morrison@ggc.scot.nhs.uk

Clinical Trial Coordinator

John McQueen
Cancer Research UK Clinical Trials Unit
Level 0
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow G12 0YN, UK
Tel: 0141 301 7191
Fax: 0141 301 7946
Email: john.mcqueen@glasgow.ac.uk

Clinical Trial Monitor

Stacey Chapman
Cancer Research UK Clinical Trials Unit
Administration Building Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH, UK
Tel: 0141 232 2117
Email: Stacey.chapman@glasgow.ac.uk

Pharmacovigilance Manager

Jaqueline Gourlay
Cancer Research UK Clinical Trials Unit
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow G12 0YN, UK
Tel: 0141 211 3052
Fax: 0141 232 2157
Email: mvls-ctu-pv@glasgow.ac.uk

Email: jacquelne.gourlay@glasgow.ac.uk

Lead Clinical Research Nurse

Ms Ruth Boyd
CRUK Senior Nurse
NI Cancer Trials Network
East Podium, C-Floor
Belfast City Hospital
Lisburn Road
Belfast BT9 7AB
Tel: 02890 638468
Fax: 02890 637743.
Email: ruth.boyd@belfasttrust.hscni.net

Funder Details

Cancer Research U.K.
Nicola Keat
Research Funding Manager
Angel Building
407 St John Street
Greater London EC1V 4AD
Email: Nicola.Keat@cancer.org.uk

Patient Public Involvement Contact

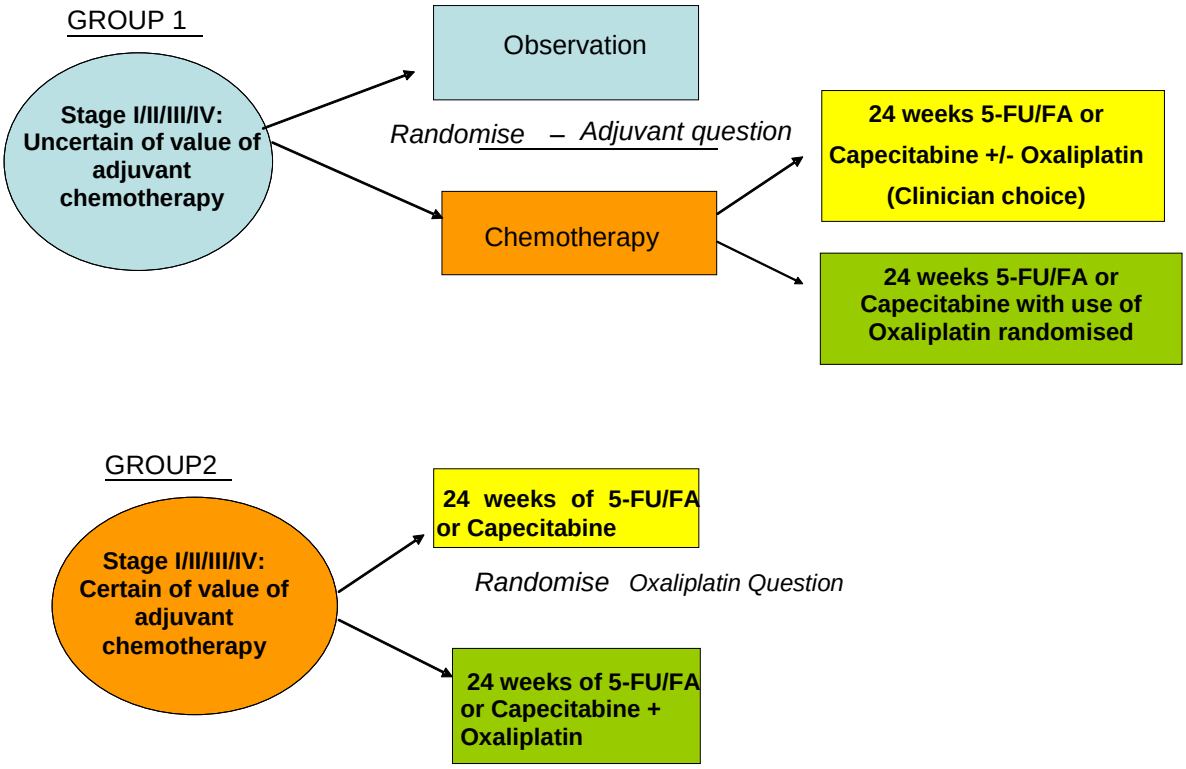
Dr Edward Goodall
N. Ireland Cancer Research Consumers' Forum
c/o NI Cancer Trials Centre
Belfast City Hospital
Lisburn Road
Belfast BT9 7AB
Email: edwardagoodall@hotmail.com

Co-Investigator

Dr Helen Coleman
Senior Lecturer in Cancer Epidemiology
Centre for Public Health
Queen's University Belfast
Belfast BT12 6BJ
Tel: 028 9097 8953
E-mail: h.coleman@qub.ac.uk

Study Schema for the BALLAD UK trial

A trial to evaluate the potential **B**enefit of **A**djuvant chemotherapy for sma**LL** bowel **AD**enocarcinoma



For Group 1 and Group 2 the choice of fluoropyrimidine will be made prior to randomisation.

In addition for Group 1 the choice of whether Oxaliplatin will be given or not or whether this will be randomised will be made prior to randomisation

Trial Summary

Title: BALLAD UK: A trial to evaluate the potential benefit of adjuvant chemotherapy for small bowel adenocarcinoma (IRCI-002). The UK component of the GLOBAL BALLAD pooled data analysis

Design: An open-label, randomised, controlled, multi-centre, trial with disease free survival as the primary endpoint. Data from BALLAD UK will be pooled with data generated from a number of different, individual, parallel prospective studies addressing the same objectives with similar designs brought together under the framework of the International Rare Cancer Initiative. This worldwide data collaboration is referred to as GLOBAL BALLAD. This protocol is for BALLAD UK, which is the component of GLOBAL BALLAD led from the UK. Other countries contributing data to GLOBAL BALLAD will develop their own protocol and put in place their own sponsorship arrangements and be responsible for trial management and safety reporting for the trials they develop.

Objectives: 1. Assessment of the efficacy of observation versus 24 weeks of adjuvant post-operative chemotherapy in resected stage I-IV small bowel adenocarcinoma (SBA).

2. Assessment of the efficacy of 24 weeks of adjuvant post-operative fluoropyrimidine 'monotherapy' regimen versus fluoropyrimidine plus Oxaliplatin combination chemotherapy regimen in resected stage I-IV small bowel adenocarcinoma (SBA).

Endpoints: Primary Endpoint

Disease free survival (defined as time from randomisation to recurrence, development of new primary or death from any cause).

Secondary Endpoints

Overall survival, cost-effectiveness, toxicity, clinico-pathological, epidemiological and molecular profiling of SBA.

Population: Patients with SBA that has been potentially cured surgically.

Eligibility: Inclusion Criteria

1. R0 resected stage I, II, III or IV SBA
2. No evidence of residual or metastatic disease at laparotomy or on CT/MRI imaging of chest, abdomen and pelvis.
3. Patients must be registered and randomised within 14 weeks of surgery and commence chemotherapy within 16 weeks of surgery
4. ECOG Performance Status of 0 or 1
5. Absolute neutrophil account ≥ 1.5 $x10^9/l$

6. Platelet count ≥ 100 x 10^9/l
7. Haemoglobin ≥90 g/l (previous transfusion is allowed)
8. AST and ALT ≤ 2.5 x upper limit of normal (ULN). (At least one of ALT or AST MUST be performed)
9. Creatinine clearance > 50 ml/min (calculated by Cockcroft Gault or Wright equation) or measured by EDTA
10. Serum bilirubin ≤ 1.5 x ULN
11. Signed and dated informed consent indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrolment.
12. Age ≥ 16 years
13. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other trial procedures.

Exclusion Criteria

1. Non-adenocarcinoma histology of small bowel tumour which includes but is not confined to lymphoma, GIST, carcinoid or other neuroendocrine tumour, squamous carcinoma, melanoma or sarcoma.
2. Adenocarcinoma arising in the appendix or colorectum
3. Previous neo-adjuvant chemo(radio)therapy for SBA
4. Clinically significant cardiovascular disease (i.e. active or < 12 months since cerebrovascular accident, myocardial infarction, unstable angina, New York Heart Association [NYHA] grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension)
5. Pregnancy/lactation or of child bearing potential and not using medically approved contraception. (Postmenopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential)
6. Previous invasive or non-invasive malignancy except:
   (i) Ductal Carcinoma In Situ (DCIS) of the breast where treatment consisted of resection alone, (ii) Cervical carcinoma in situ where treatment consisted of resection alone, (iii) Basal cell or squamous cell carcinoma where treatment consisted of resection alone or radiotherapy, (iv) Superficial bladder carcinoma where treatment consisted of resection alone or with a single installation of intravesical chemotherapy or with BCG treatment, (v) Other cancers where the patient has been disease-free for at least 3 years and treatment was with curative

intent, and (vi) Other cancers with very low potential for recurrence can be discussed with the CI or his approved representative through the Glasgow CRUK Clinical Trials Unit where eligibility will be considered on an individual basis.

7. Complete dihydropyrimidine dehydrogenase (DPD) deficiency. Patients with partial DPD deficiency (characterised by certain heterozygous DPYD variants) may still be eligible for study treatment with fluorouracil or oral capecitabine with reduced starting doses based on the latest guidance available (see Section 5.1).
8. Known untreated coeliac disease (may be enrolled if diet controlled), untreated chronic inflammatory bowel disease or other cause of malabsorption or intestinal obstruction
9. Grade ≥ 2 peripheral neuropathy
10. Administration of any investigational drug within 28 days or 5 half-lives, whichever is longer, prior to receiving the first dose of trial treatment.
11. Previous hypersensitivity to platinum salts
12. Patients with clinically significant, active infections, or any other serious medical condition in which chemotherapy is contraindicated will be excluded
13. Patients with untreated vitamin B12 deficiency are excluded from receiving folinic acid as part of their chemotherapy regimen. However, these patients may be eligible for treatment with capecitabine fluoropyrimidine therapy, where no folinic acid is administered as part of the treatment regimen
14. Patients with clinically significant sensorineural hearing impairment are excluded from receiving oxaliplatin but will be eligible for the fluoropyrimidine monotherapy provided as a clinician's choice for patients in group 1 randomised to either observation or chemotherapy
15. Any patient receiving treatment with brivudine, sorivudine and analogues within 4 weeks prior to receiving the first dose of trial capecitabine or 5-FU.

Treatment: Group 1 patients, where there is uncertain value of adjuvant chemotherapy, will be randomised to observation versus chemotherapy. The chemotherapy will be 24 weeks fluoropyrimidine

with or without Oxaliplatin or these patients can be randomised to receive Oxaliplatin or not as per Group 2 patients below. The choice of chemotherapy must be specified prior to randomisation.

Group 2 patients, where there is certain value of adjuvant chemotherapy, will be randomised to receive 24 weeks fluoropyrimidine chemotherapy either with or without Oxaliplatin. The choice of fluoropyrimidine must be specified prior to randomisation.

Duration: Patients will be recruited into the trial over a period of 5 years and have a period of follow-up for up to 7 years.

Schedule of Assessments – Patients randomised to Observation Only

	Screening					Follow Up						
Trial Procedures	**≤28 days prior to Reg/Rand**	**≤7 days prior to Reg/Rand**	**Reg/Rand**	**Month 3 Post Randomisation**	**Month 6 post randomisation**	**Month 9 post reg/rand**	**Month 12 post reg/rand**	**Month 18 post reg/rand**	**Month 24 post reg/rand**	**Month 30 post reg/rand**	**Month 36 post reg/rand**	**Annually until 7 yrs post reg/rand**
Informed Consent [1]	✓											
Review of Eligibility Criteria		✓										
Medical History		✓										
Physical/Clinical Assessment (inc height and weight, BP, Pulse, assessment of neuropathy and assessment of sensorineural hearing impairment)		✓		✓	✓							
Body Surface Area		✓										
ECG[2]		✓										
ECOG Performance Status		✓										
Surgery[3]	To be within 14 weeks of randomisation											
Laboratory Procedures												
Haematology (Co-ag) [4]		✓[5]										
Haematology (FBC)		✓[5]		✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]
Urea & Electrolytes		✓[5]		✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]
Liver Function Tests [7]		✓[5]		✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]	✓[5]
Magnesium and estimated GFR		✓[5]										
Urine Pregnancy Test		✓										
Radiological Assessment												
CT Scan (chest, abdomen and pelvis) [8]	To be within 12 weeks pre-trial entry						✓[9]		✓[9]		✓[9]	
Patient Questionnaires												
EORTC QLQ-C30 & CR29 QoL		✓		✓[10]	✓	✓[10]	✓	✓	✓			
EQ-5D		✓		✓[10]	✓	✓[10]	✓	✓	✓	✓	✓	✓
Translational Research												
Tissue collection [11]	✓											
Blood Sample collection [12]		✓										
DPD Deficiency Testing[14]	✓											

Schedule of Assessments – For patients randomised to 5-FU/FA +/- Oxaliplatin

	Screening			Treatment Cycle												Follow Up						
Trial Procedures	**≤28 days prior to Reg/Rand**	**≤7 days prior to Reg/Rand**	**Reg/Rand**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9**	**Cycle 10**	**Cycle 11**	**Cycle 12**	**Moth 9 post reg/rand**	**Moth 12 post reg/rand**	**Moth 18 post reg/rand**	**Moth 24 post reg/rand**	**Month 30 post reg/rando**	**Moth 36 post**	**Annually until 7 yrs post**
Informed Consent [1]	✓																					
Review of Eligibility Criteria		✓																				
Medical History		✓																				
Physical/Clinical Assessment (inc height and weight, BP pulse, assessment of neuropathy and assessment of sensorineural hearing impairment)		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓							
Body Surface Area		✓																				
ECG[2]		✓																				
ECOG Performance Status		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓							
Toxicity Assessment				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓							
Administration of IMP[13]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓							
Surgery[3]	To be within 16 weeks of cycle 1 date																					
Laboratory Procedures																						
Haematology (Clotting [4])		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]							
Haematology (FBC)		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]
Urea & Electrolytes		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]
Liver Function Tests [7]		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]
Magnesium and GFR		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6	✓[6]	✓[6]	✓[6]							
Urine Pregnancy Test		✓[5]																				
Radiological Assessment																						
CT Scan (chest, abdomen and pelvis) [8]	To be within 12weeks pre-trial																✓[9]		✓[9]		✓[9]	
Patient Questionnaires																						
EORTC QLQ-C30 & CR29 QoL		✓							✓						✓	✓	✓	✓	✓			
EQ-5D		✓							✓						✓	✓	✓	✓	✓	✓	✓	✓
Translational Research																						
Tissue collection [11]	✓																					
Blood Sample collection [12]		✓																				
DPD Deficiency Testing[14]	✓																					

Schedule of Assessments – For patient randomised to Capecitabine +/- Oxaliplatin

	Screening			Treatment Cycle								Follow Up						
Trial Procedures	**≤28 days prior to Reg/Rand**	**≤7 days prior to Reg/Rand**	**Reg/Rand**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Moth 9 post reg/rand**	**Moth 12 post reg/rand**	**Moth 18 post reg/rand**	**Moth 24 post reg/rand**	**Moth 30 post reg/rand**	**Moth 36 post reg/rand**	**Annually until 7 yrs post reg/rand**
Informed Consent [1]	✓																	
Review of Eligibility Criteria		✓																
Medical History		✓																
Physical/Clinical Assessment (inc height and weight BP, pulse, assessment of neuropathy and assessment of sensorineural hearing impairment)		✓		✓	✓	✓	✓	✓	✓	✓	✓							
Body Surface Area		✓																
ECG[2]		✓																
ECOG Performance Status		✓		✓	✓	✓	✓	✓	✓	✓	✓							
Toxicity Assessment				✓	✓	✓	✓	✓	✓	✓	✓							
Administration of IMP[13]				✓	✓	✓	✓	✓	✓	✓	✓							
Surgery[3]	To be within 16 weeks of cycle 1 date																	
Laboratory Procedures																		
Haematology (Clotting [4])		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]							
Haematology (FBC)		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]
Urea & Electrolytes		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]
Liver Function Tests [7]		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]
Magnesium and GFR		✓[5]		✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]	✓[6]							
Urine Pregnancy Test		✓[5]																
Radiological Assessment																		
CT Scan (chest, abdomen and pelvis) [8]	To be within 12 weeks pre-trial entry												✓[9]		✓[9]		✓[9]	
Patient Questionnaires																		
EORTC QLQ-C30 & CR29 QoL		✓					✓				✓	✓	✓	✓	✓			
EQ-5D		✓					✓				✓	✓	✓	✓	✓	✓	✓	✓
Translational Research																		
Tissue collection [11]	✓																	
Blood Sample collection [12]		✓																
DPD Deficiency Test[14]	✓																	

(1) All patients must be consented to the trial prior to randomisation and prior to any treatment starting.
(2) A baseline ECG should be performed within 7 days of randomisation, however ECGs performed up to 20 days prior to randomisation will be accepted.
(3) Patients should be randomised within 14 weeks of surgery and treatment should start within 2 weeks of randomisation date. However as long as the surgery to cycle 1 treatment start date is ≤ 16 weeks the patient will be considered eligible. Please contact your co-ordinating trials office for clarification.
(4) Coagulation tests only required to be performed in patients on treatment with anti-coagulants after baseline.
(5) Pre-randomisation and C1 bloods should preferably be taken within 7 days prior to randomisation/C1 date, but bloods taken up to a maximum of 9 days pre-randomisation/C1 date will be accepted
(6) From cycle 2 onwards, pre-cycle bloods should be performed within 2 days of day 1 of a treatment cycle. Bloods taken for a follow-up visit may be completed within one month prior to the scheduled visit. Once the primary endpoint of disease free survival has been reached FBC and biochemistry tests are no longer required. Pre-cycle (excluding pre-randomisation) blood tests may be completed locally / at a patient's GP. The blood test results must be signed dated and filed in patient notes for source verification.
(7) At least one of AST or ALT must be performed to assess liver function.
(8) CT scan is the preferred method of radiological assessment, however it is acceptable to use MRI of abdomen and pelvis and chest CT. The baseline CT scan should be performed within 12 weeks of the date of randomisation. Additional CT scans can be performed at any stage during the trial if clinically indicated
(9) CT Scans performed up to 42 days prior to the scheduled follow up visit date will be accepted and used for that follow up visit.
(10) Quality of life assessments at 3 and 9 months should be posted to patient's home for completion for patients randomised to observation only
(11) For those patients who have consented to tumour sample collection, paraffin embedded tumour tissue obtained at surgical resection of the primary tumour prior to entry to BALLAD UK should be collected. Further instructions will be available in a separate translational research manual
(12) For those patients who have consented to blood sample collection. Bloods should be collected prior to the start of therapy. Further instructions will be available in a separate translational research manual
(13) All drugs administered as part of the Group 1 & 2 randomisations are considered Investigational Medicinal Products (IMPs) for the purposes of this protocol.
(14) Should be performed at any time prior to randomisation if standard of care or clinically indicated

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List of Abbreviations

5-FU	5-Fluorouracil
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AR	Adverse Reaction
ASCO	American Society Of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
CEA	Carcinoembryonic Antigen
CI	Chief Investigator
CRC	Colorectal Cancer
CRF	Case Report From
CRUK	Cancer Research U.K.
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTC	Clinical Trial Coordinator
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
DFS	Disease Free Survival
DMC	Date Monitoring and Ethics Committee
DPD	Dihydropyrimidine Dehydrogenase
DYPD	gene encoding dihydropyrimidine dehydrogenase
DSUR	Developmental Safety Update Report
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FAP	Familial Adenomatous Polyposis
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular filtration rate
GI	Gastro-intestinal
GP	General Practitioner
HE	Health Economic
HNPCC	Hereditary non-polyposis colorectal cancer
HR	Hazard Ratio

IMP	Investigational Medicinal Product
IRCI	International Rare Cancer Initiative
ISF	Investigator Site File
ITT	Intention to Treat
IV	Intravenous
LFT	Liver Function Test
LNR	Lymph Node Ratio
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCRN	National Cancer Research Network
NIMP	Non Investigational Medicinal Product
NYHA	New York Heart Association
OS	Overall Survival
PI	Principal Investigator
PICC	Peripherally Inserted Central Catheter
PLN	Positive Lymph Nodes
PO	Oral
PV	Pharmacovigilance
QoL	Quality of Life
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBA	Small Bowel Adenocarcinoma
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDS	Three times daily (ter die sumendus)
TLN	Total number of Lymph Nodes
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea and Electrolytes
ULN	Upper Limit of Normal

1 INTRODUCTION

1.1 Background

Small bowel adenocarcinoma (SBA) is a rare cancer, representing less than 5% of gastrointestinal cancers, with approximately 2,000 new cases of SBA and 1,100 deaths from this in the United States in 2008 (1, 2). 60-70% of SBA cancers are potentially curable (i.e. stages I – III). The annual incidence of SBA is about 2.2 - 5.7 per million inhabitants in Western countries. The incidence of SBA is increasing, particularly those with a duodenal location. The incidence of SBA is higher in industrialised countries, increases with age, and is more frequent in males than females. Those of Afro-Caribbean descent have a significantly higher incidence rate than other racial groups. Adenocarcinomas are mostly distributed proximally in the small intestine, with approximately 45% within the duodenum, 35% in the jejunum and 20% in the ileum. One of the most important known risk factors in the pathogenesis of SBA is previous Crohn's disease. The risk for developing SBA is increased in patients with coeliac disease (relative risk, 60- to 80-fold) but the mechanisms that predispose coeliac disease patients to SBA are not known. SBA is also associated with Familial Adenomatous Polyposis (FAP), Peutz-Jeghers syndrome, hereditary non-polyposis colorectal cancer (Lynch syndrome), cystic fibrosis and peptic ulceration. Behavioural risk factors include consumption of red meat, smoked and salt-cured foods and saturated fat, obesity and smoking

The clinical presentation and diagnosis of SBA is usually delayed, with an average delay of six to eight months from onset of symptoms. This is primarily because small bowel tumours are not accessible by endoscopic examination, especially when they are distal to the second part of the duodenum. Because of the non-specific nature of presenting clinical manifestations and the lack of effective tools for exploring the small bowel, SBA is usually diagnosed at an advanced stage. Most commonly, patients present with signs and symptoms of obstruction, though anaemia with haemoccult-positive stools is also a frequent occurrence. SBA can be diagnosed through an upper GI or small intestine oral contrast follow-through study or CT scan. Recently, capsule endoscopy has been used in the diagnosis of such tumours. Histological confirmation can be obtained via an upper gastrointestinal endoscopy, with total duodenoscopy in duodenal lesions, but the diagnosis remains obscure for most distal lesions until laparotomy.

SBA carries a poor prognosis at all stages (I, II, III and IV). For SBA patients who undergo potentially curative resection, there is a 40-65% 5 year overall survival (OS); whereas, for those who have a non-curative resection, it is only 15-30%. Experience of potentially curative (R0) resection of metastatic SBA is much more limited than that for colorectal cancer, but long term data in case series and registries supports this strategy in appropriate patients, and the value of post-operative chemotherapy in this setting needs to be investigated.

Stage I (incidence 5%): 50-60% 5 year overall survival.

Stage II (incidence 25-40%): 40-50% 5 year overall survival.

Stage III (incidence 25-40%): 25-35% 5 year overall survival.

Stage IV (incidence 30-40%): 3-5% 5 year overall survival.

Lymph node metastases are frequently present at time of presentation of SBA, and thus a curative resection should generally include a systematic regional lymphadenectomy regardless of the primary tumour location. Survival after surgical resection for stage I, II, and III SBA was associated with the total number of resected lymph nodes (TLNs) assessed in various studies (4). Stratifying patients with stage III disease by number of positive lymph nodes (PLNs) into those with <3 PLNs and ≥3 PLNs significantly improved prognostication. The lymph node ratio (LNR), which is the number of PLNs to TLNs (3), is also important. When ≥10 nodes were recovered, OS rate increased non-significantly in stage I (73.2% vs. 55.6%) and significantly in stage II (61.8% vs. 32.9%, $p < 0.001$) but was unchanged in stage III (27.4% vs. 27.3%, $p = 0.13$). Recovery of ≥10 nodes occurred in 26.9%, 23.6%, and 42.1% of patients with stage I, II, and III SBA, respectively. Multivariate analysis identified age, American Joint Committee on Cancer (AJCC) stage, site of primary tumour, recovery of ≥10 lymph nodes, and number of positive nodes as significant for OS (5).

1.2 Adjuvant Therapy

To date, no standard adjuvant regimen has been defined because of the absolute absence of randomised controlled trials in this disease and hence a reliance on retrospective review of single centre series. Even after potentially curative resection, over half of the patients will succumb to distant metastases and die of the disease so there is a clear rationale to explore the use of adjuvant therapy in SBA. Correlation with the proven benefits of adjuvant therapy in colorectal cancer (CRC) and other solid tumours suggest that use of adjuvant therapy may be worthwhile in SBA.

As regards retrospective review of case series, there is some information on prognostic factors. In one series, patients who received adjuvant therapy had significantly higher tumour stage and rate of lymph node involvement. Five-year Disease Free Survival (DFS) and OS did not differ between treatment groups (4). In multivariate analysis, the use of adjuvant therapy was associated with improved DFS (HR 0.27; 95% Confidence interval 0.07–0.98, $p = 0.05$) but not OS (HR 0.47; 95% Confidence interval 0.13–1.62, $p = 0.23$). In patients with a high risk of relapse (defined as a lymph node ratio ≥10%), adjuvant therapy appeared to improve OS ($p = 0.04$), but not DFS ($p = 0.15$). The prognostic factors determined from this study are in agreement with the generally accepted poor prognostic factors in SBA, which include pT4 tumour stage, worse histological differentiation, positive resection margins, lymphovascular invasion and lymph node involvement

The rationale to investigate adjuvant chemotherapy in SBA has been based upon the known pattern of failure following surgical resection, the reported activity of systemic chemotherapy in patients with advanced SBA and by correlation with the evidence base from adjuvant treatment of CRC. In patients with advanced disease, modern chemotherapy combinations of 5-fluorouracil (5-FU) and a platinum agent have demonstrated significant activity, with response rates ranging from 29 to 50% (6, 7, 8).

In retrospective series that have evaluated the pattern of initial disease recurrence following surgical resection of SBA, distant relapse occurred in 81 - 100% of cases, while local relapse occurred in 0 - 29% of cases. In the subset of patients with adenocarcinoma of the duodenum, the rate of local relapse is higher, but systemic relapse still predominates.

A number of single institution retrospective studies have evaluated the role of adjuvant chemotherapy for SBA, but none of these studies have shown a statistically significant benefit favouring its use. Separate retrospective studies have evaluated the role of adjuvant chemoradiation following resection of adenocarcinoma of the duodenum, but again none have demonstrated a clear benefit for adjuvant treatment. The inability to control for the various prognostic factors influencing the original decision to administer adjuvant therapy has been a major limitation of these studies, as patients who receive adjuvant therapy tend to be those at higher risk for disease recurrence (based on currently used prognostic factors).

A study of 75 cases of primary malignant tumours of the small bowel stated that chemotherapy had no effect on prognosis (9). Similar conclusions were drawn from a series of 217 patients where adjuvant chemotherapy did not improve overall survival after potentially curative surgical resection of SBA (10). The results may be due to the small number of patients treated, with only 59 patients (27%) being treated with adjuvant chemotherapy. No data was available on the type of chemotherapy used.

A retrospective review involving 491 patients with SBA diagnosed at the Mayo clinic between 1970 and 2005 (11) found that the 5-year OS for patients with stage I, II, and III disease was 80%, 44% and 25% respectively. Seventy-five patients received either adjuvant chemotherapy or chemoradiation. No clear benefit for adjuvant treatment use was seen. The 5-year OS for patients who received adjuvant therapy was 39% compared to 36% for those who did not (P=0.44). The authors comment that the relatively small number of patients receiving adjuvant therapy, the wide range of chemotherapy regimens used and evolving radiotherapy techniques limit the applicability of this observation. In a multivariate analysis age, stage and lymph node ratio ($\geq$50% v <50%) were found to be prognostic for OS.

In a retrospective series of 64 patients from Roswell Park Cancer Institute, 30 patients underwent margin-negative resections and 11 of these patients received adjuvant chemotherapy (12). Median OS for those patients who did and did not receive adjuvant chemotherapy were 56 and 41 months, respectively, though no statistical comparison was conducted. A second study from the Princess Margaret Hospital reported on 60 patients who underwent curative-intent surgery with unknown margin status (13). Fifteen patients (25%) received adjuvant chemotherapy, with a median OS of 22 months compared with 28 months for the non-adjuvant treatment group. However, patients receiving adjuvant therapy were more likely to have lymph node involvement and poor histological differentiation compared with patients who did not receive adjuvant treatment.

Despite the lack of evidence supporting the delivery of adjuvant chemotherapy for SBA, an analysis in the USA of the National Cancer Database has shown an increase in use from 8% in 1985 to 24% in 2005 (2). Anecdotal evidence throughout the developed world suggests that this has continued to significantly increase since 2005. The reported efficacy of fluoropyrimidine monotherapy, capecitabine and oxaliplatin in CAPOX, mixed bolus/infusional 5-FU and folinic acid with oxaliplatin in FOLFOX and mixed bolus/infusional 5-FU and folinic acid with irinotecan in FOLFIRI in advanced SBA suggest these regimens could be investigated in trials of adjuvant therapy for patients who undergo potentially curative surgical resection of SBA. The more limited efficacy of irinotecan than oxaliplatin combinations in advanced SBA (8), the high reported response rate seen with capecitabine and oxaliplatin in a phase II trial in advanced SBA (7) and the failure to significantly improve survival by the addition of irinotecan, bevacizumab and cetuximab to fluoropyrimidines in the adjuvant chemotherapy of CRC are relevant. These data suggest that these regimens should not be studied in the adjuvant setting in SBA at this time, but that the role of intravenous (IV) or oral (PO) fluoropyrimidines both as monotherapy and in combination with oxaliplatin should be.

1.3 The Need for a Trial

This is the first SBA trial to emerge from the International Rare Cancer Initiative (IRCI). The IRCI was established early in 2011 between Cancer Research U.K. (CRUK) and the National Cancer Research Network (NCRN) in the UK, the National Cancer Institute (NCI) in the US and the European Organisation for Research and Treatment of Cancer (EORTC) in Europe, with other international cancer clinical trials organisations subsequently joining [such as the Canadian Cancer Trials Group (CCTG), French National Cancer Institute (INCa), Japan Clinical Oncology Group (JCOG) and the Clinical Oncology Society of Australia (COSA)] and with others showing an interest also. Their objective is to initiate and aid the development of international clinical trials for rare cancers. This trial has been developed under those auspices in collaboration with international colleagues. It is intended to run as an international trial, and various European and other countries are all committed in their support.

Although BALLAD UK is the flagship trial addressing these questions in SBA, a number of other parallel studies with the same underlying design features and endpoints will be undertaken in other countries and jurisdictions. There is a prospective agreement in place to pool the results from these studies in order to achieve the total sample size specified in the BALLAD UK protocol. These studies collectively make up the GLOBAL BALLAD collaboration. In July 2018, the GLOBAL BALLAD collaboration included open adjuvant randomised controlled trials in the UK, France and Japan, with trials in set-up or in development in Denmark, the Republic of Ireland, Belgium and the Netherlands.

The utility of adjuvant chemotherapy in the management of SBA remains unproven and awaits the results of a large, global, prospective, phase III, randomised, controlled trial. Across the 830 million population of North America and Europe, there are approximately 3,000 patients with R0 resected and

potentially cured SBA every year who would be potentially eligible for such an adjuvant chemotherapy trial. An initial meeting on SBA through the IRCI SBA Working Group was held at the American Society of Clinical Oncology (ASCO) meeting in June 2011 as part of the IRCI with representation from funders and investigators for all the organisations, with subsequent teleconferences and further face-to-face meetings at GI ASCO and ASCO in both January and June annually since then, and most recently in June 2018. Given the absence of good-quality and evidence-based data, it has been agreed that a trial considering adjuvant chemotherapy versus no chemotherapy was appropriate for patients with stage I-IV SBA in whom the oncologist and patient feel that the benefit of adjuvant chemotherapy is uncertain. For those patients with stage I-IV SBA who, with their oncologists, feel that the potential benefit of adjuvant chemotherapy is certain (and hence are not willing to accept randomisation to the 'no chemotherapy' arm), a randomisation between single agent fluoropyrimidine versus doublet fluoropyrimidine and oxaliplatin chemotherapy will be offered. Tumour stage will be used as a stratification factor. Those patients who do not consent to be randomised will be offered registration to allow collection of demographic, clinicopathological, epidemiological and survival data, thereby making optimal use of the rare patient population available. In addition, archival Formalin Fixed Paraffin Embedded (FFPE) tissue and contemporaneous venous blood samples will be collected from every registered patient to allow molecular profiling and future translational research. A questionnaire about underlying risk factors (e.g. Crohn's disease, coeliac disease, Lynch syndrome etc.) will be completed along with the other collected data on all registered patients.

1.4 Trial Hypothesis

The trial hypotheses are that:

1. Adjuvant chemotherapy results in an improved outcome (DFS and OS) over observation alone after potentially curative R0 surgery for stage I, II, III and IV SBA
2. Adjuvant fluoropyrimidine and oxaliplatin chemotherapy results in an improved outcome (DFS and OS) over fluropyrimidine alone after potentially curative R0 surgery for stage I, II, III and IV SBA

2 TRIAL OBJECTIVES

2.1 Primary Objective

- Assess the efficacy of observation against 24 weeks of adjuvant post-operative chemotherapy
- Assessment of the efficacy of 24 weeks of adjuvant post-operative 5-FU/Capecitabine monotherapy versus 5-FU/Capecitabine plus Oxaliplatin

2.2 Secondary Objectives

- Assess the toxicity of chemotherapy, the cost-effectiveness of the treatment alternatives and establish a central tissue and data bank for patients with this rare cancer.

3 TRIAL DESIGN

This is an open-label, randomised controlled, multi-centre, trial with disease free survival as the primary endpoint.

This protocol is specifically for the component of GLOBAL BALLAD led from the UK. It is expected that other countries contributing to providing data for GLOBAL BALLAD will be responsible for developing their own trials, with their own local sponsorship and safety reporting arrangements. The CRUK Glasgow CTU will act as the secretariat for the data gathered for the GLOBAL BALLAD collaboration. Trial data from all the participating studies will be sent to CRUK Glasgow CTU for analysis.

The GLOBAL BALLAD collaboration responsibilities are documented in the GLOBAL BALLAD Charter which all the Chief Investigators from the collaborating studies will sign.

The GLOBAL BALLAD design incorporates a frequentist approach and a Bayesian combination of the observed data with clinician's prior beliefs to provide final estimates of the treatment effect (see section 7).

This BALLAD UK trial will be performed according to the UK Policy Framework for Health and Social Care and the Medicines for Human Use (Clinical Trials) Regulations (2017) and The Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2004:1031 (as amended). All investigators and key trial personnel will be appropriately trained in Good Clinical Practice (GCP).

3.1 Trial Population

Patients with R0 resection of stages I, II, III or IV small bowel adenocarcinoma.

The target recruitment of BALLAD UK is 120 patients.

3.2 Inclusion Criteria

1. R0 resected stage I, II, III or IV small bowel adenocarcinoma (SBA)
2. No evidence of residual or metastatic disease at laparotomy and CT/MRI imaging of chest, abdomen and pelvis.
3. Patients must be registered and randomised within 14 weeks of surgery and commence chemotherapy within 16 weeks of surgery
4. ECOG Performance Status of 0 or 1
5. Absolute neutrophil account ≥ 1.5 $x10^9$/l
6. Platelet count ≥ 100 x 10^9/l
7. Haemoglobin ≥90 g/l (previous transfusion is allowed)
8. AST and ALT ≤ 2.5 x upper limit of normal (ULN). (At least one of ALT or AST MUST be performed)

9. Creatinine clearance > 50 ml/min (calculated by Cockcroft Gault or Wright equation) or measured by EDTA
10. Serum bilirubin ≤ 1.5 x ULN
11. Signed and dated informed consent indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrolment.
12. Age ≥ 16 years
13. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other trial procedures.

3.3 Exclusion Criteria

1. Non-adenocarcinoma histology of small bowel tumour which includes but is not confined to lymphoma, GIST, carcinoid or other neuroendocrine tumour, squamous carcinoma, melanoma or sarcoma.
2. Adenocarcinoma arising in the appendix or colorectum
3. Previous neo-adjuvant chemo(radio)therapy for small bowel adenocarcinoma
4. Clinically significant cardiovascular disease (i.e. active or < 12 months since cerebrovascular accident, myocardial infarction, unstable angina, New York Heart Association [NYHA] grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension)
5. Pregnancy/lactation or of child bearing potential and not using medically approved contraception. (Postmenopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential)
6. Previous invasive or non-invasive malignancy except:
   (i) Ductal Carcinoma In Situ (DCIS) of the breast where treatment consisted of resection alone, (ii) Cervical carcinoma in situ where treatment consisted of resection alone, (iii) Basal cell or squamous cell carcinoma where treatment consisted of resection alone or radiotherapy, (iv) Superficial bladder carcinoma where treatment consisted of resection alone or with a single installation of intravesical chemotherapy or with BCG treatment, (v) Other cancers where the patient has been disease-free for at least 3 years and treatment was with curative intent, and (vi) Other cancers with very low potential for recurrence can be discussed with the CI or his approved representative through the Glasgow CRUK Clinical Trials Unit where eligibility will be considered on an individual basis.
7. Complete dihydropyrimidine dehydrogenase (DPD) deficiency. Patients with partial DPD deficiency (characterised by certain heterozygous DPYD variants) may still be considered for study treatment with fluorouracil or oral capecitabine with reduced starting doses based on the latest guidance available (see Section 5.1).
8. Known untreated coeliac disease (may be enrolled if diet controlled), untreated chronic inflammatory bowel disease or other cause of malabsorption or intestinal obstruction

9. Grade ≥ 2 peripheral neuropathy
10. Administration of any investigational drug within 28 days or 5 half-lives, whichever is longer, prior to receiving the first dose of trial treatment.
11. Previous hypersensitivity to platinum salts
12. Patients with clinically significant active infections, or any other serious medical condition in which chemotherapy is contraindicated will be excluded
13. Patients with untreated vitamin B12 deficiency are excluded from receiving folinic acid as part of their chemotherapy regimen. However, these patients may be eligible for treatment with capecitabine fluoropyrimidine therapy, where no folinic acid is administered as part of the treatment regimen
14. Patients with clinically significant sensorineural hearing impairment are excluded from receiving oxaliplatin but will be eligible for the fluoropyrimidine monotherapy provided as a clinician's choice for patients in group 1 randomised to either observation or chemotherapy
15. Any patient receiving treatment with brivudine, sorivudine and analogues within 4 weeks prior to receiving the first dose of trial capecitabine or 5-FU.

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria should be addressed via contact with the CRUK Clinical Trials Unit (CTU) Glasgow prior to calling for registration/randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply

3.4 Identification of Participants and Consent

All potentially eligible SBA patients should be approached to take part in the randomised trial. Patients will be given at least 24 hours to consider participation and the opportunity to ask questions. Patients will also be made aware that they can withdraw from the trial at any time for any reason without their standard of care being affected. No trial related activities can take place prior to consent being obtained.

If a patient is unwilling or ineligible to enter the randomised trial they should be asked if they would consent to patient registration for tissue acquisition only, this is described in section 3.6. This would allow for the collection of demographic, clinic-pathological and survival data on these patients.

3.5 Randomisation

For those patients willing to be randomised; the randomisation options depend on the patient group:

Group 1: R0 resected stage I/II/III/IV patients where there is uncertainty of the value of adjuvant chemotherapy

Patients in this group will be randomised 1:1 to adjuvant chemotherapy or observation. An initial choice must be made by the clinician or patient whether, if allocated to chemotherapy, they will receive either:

a) 24 weeks of intravenous 5-FU/FA or oral capecitabine

b) 24 weeks of intravenous 5-FU/FA or oral capecitabine + intravenous oxaliplatin

c) Either a or b allocated at random

For all options the fluoropyrimidine choice must be specified prior to randomisation (1:1)

For patients that are going into the observation v chemotherapy randomisation with the clinician's choice of chemotherapy being used they should be consented and randomised to the study using patient information sheet A

For patients that are going into the observation v single agent chemo v double agent chemotherapy randomisation, i.e. will be contributing to both groups, they should be consented and randomised to the study using patient information sheet B

Group 2: R0 resected stage I/II/III/IV patients where there is certainty of the value of adjuvant chemotherapy.

Patients in this group will be randomised 1:1 to 24 weeks of fluoropyrimidine based adjuvant chemotherapy with or without oxaliplatin. The choice of 5-FU/FA or Capecitabine must be specified prior to randomisation.

For patients that are going into the single agent v double agent chemotherapy randomisation they should be randomised using patient information sheet C

To register/randomise a patient on the trial, contact the CRUK Glasgow CTU. Registration/Randomisation to the trial can be performed by either telephone, fax or email using the following details:

Telephone Number: 0141 301 7195

Fax Number: 0141 301 7946

Email: ggc.recruitment.crukglasgowctu@nhs.scot

Randomisation service: Monday Thursday 08.30 – 17.00, Friday 08.30 – 16.30. Fax 24 hours.
(Faxes or emails received outside office hours will be dealt with the next working day.)

The patient's eligibility criteria will be checked and, if eligible, a three digit trial number will be allocated at this point.

Patients will be stratified for:

- Tumour stage
- Tumour location (jejunum and ileum or duodenum)
- Country
- Choice of preferred fluoropyrimidine (5-FU/FA or Capecitabine)
- For group 1 patients the oxaliplatin choice (if allocated to receive adjuvant chemotherapy)
    - Not to give oxaliplatin
    - To give oxaliplatin
    - To randomise whether or not the patient receives oxaliplatin

All patients must be randomised onto the trial prior to commencement of trial treatment.
The participant's GP will be informed of involvement in the trial if they have consented to this.

3.6 Patients who are registered for tissue acquisition only

Due to the rare nature of SBA we would like to collect some information on patients who are unwilling or unable to consent for the randomised trial. All patients who have R0 resected SBA with no evidence of metastasis at the time of signing consent are eligible for tissue acquisition only. This will involve the patient signing a separate registration consent form and include the collection of demographic, clinic-pathological, epidemiological and survival data. Patients who consent to registration must be registered via the telephone number above within 28 days of signing consent. In addition archival FFPE and a blood sample will be collected for these patients to allow molecular profiling and future translational research. A questionnaire about underlying risk factors (e.g. Crohn's disease, coelic disease, Lynch Syndrome etc.) will be completed also. The patients should ideally be registered and have venous blood sampling before starting adjuvant chemotherapy, but this may also be done afterwards as long as the patient has no evidence of progression at the time of sampling.

Patients who are entering the registration only part of the study should be consented using patient information sheet D.

3.7 Withdrawal

Patients have the right to withdraw for the trial at any point for any reason and investigators have the right to withdraw a patient from treatment for medical concerns. When a patient expresses a wish to withdraw it is important to determine and record whether the patient wants to stop trial treatment only or to withdraw from the trial as a whole.

3.7.1 Withdrawal of Patients from Trial Treatment

Patients have the right to withdraw from trial treatment at any point for any reason. Similarly the investigator may withdraw patients from the trial drug in the event of intra-current illness, adverse events, serious adverse events, SUSARs, protocol violations or any other relevant reasons. If a patient withdraws from treatment early they should be followed up as per trial schedule.

3.7.2 Withdrawal from Trial

The patient can decide to withdraw their consent from the trial at any time. If the patient wants to withdraw consent for the trial, then a Consent Withdrawal Form should be completed by the site and sent to the CRUK Glasgow CTU. Once a patient has withdrawn from the trial no further data will be collected on that patient and no further samples collected. It should be clearly documented in the patient's notes and the Consent Withdrawal Form what the patient is withdrawing from i.e. further data being collected or the right to use data and samples collected prior to this point.

4 TRIAL DESIGN

4.1 Trial Schedule

For Group 1 patients randomised to observation only:

Clinic visits are mandated at screening, 3 months post randomisation, 6 months post randomisation, 9 months post randomisation, 12 months post randomisation then every 6 months until 3 years post randomisation and then annually for up to 7 years post randomisation.

For Group 1 patients randomised to chemotherapy and for all Group 2 patients:

Clinic visits are mandated at screening, during treatment for chemotherapy, 9 months post randomisation, 12 months post randomisation then every 6 months until 3 years post randomisation, then annually for up to 7 years post randomisation.

4.1.1 Pre-randomisation Evaluations

- Within **14 weeks** of trial entry the patient must have had surgery. The authorised pathology report must confirm microscopically clear surgical resection margins. A FFPE archival sample of tumour must be made available to the trial team for molecular profiling and further translational research. This can be sent after the patient has been randomised.
- Within **12 weeks** of trial entry a CT chest, abdomen and pelvis or CT chest and MRI abdomen and pelvis must be performed. If this is outside the required time window it must be repeated after the patient has given written informed consent for the trial.
- Within **28 days** of registration/randomisation written, informed consent must be provided.
- Within **7 days** of trial entry the following must have occurred:
    - Review of eligibility criteria
    - Medical history
    - Physical/Clinical assessment including height and weight
    - Clinical assessment of neuropathy (baseline)
    - Clinical assessment of sensorineural hearing impairment (baseline)
    - Body Surface Area
    - ECOG performance status
    - Baseline ECG

- Haematology blood sample including coagulation profile
- Biochemistry including U&E, LFTs, magnesium and GFR
- Urine pregnancy test for all women of childbearing potential
- Baseline QoL questionnaires – EQ-5D and EORTC QLQ-C30 and CR29
- Archival blood sample for molecular profiling and future translational research
- A questionnaire about underlying risk factors (e.g. Crohn's disease, coelic disease, Lynch Syndrome etc.) will be completed at time of study entry

Any time prior to randomisation

- DPD Deficiency test if mandated as standard of care or if clinically indicated

4.1.2 Evaluations While on Trial Treatment

Prior to each cycle of chemotherapy the following tests should be performed:

- ECOG performance status
- Toxicity Assessment (only toxicities which are grade 2 or above require entry to the CRF)
- If the patient has been randomised to receive oxaliplatin treatment clinical assessment of neuropathy should be performed at all study visits
- If the patient has been randomised to receive oxaliplatin treatment clinical assessment of sensorineural hearing impairment should be performed at all study visits
- Haematology blood sample (full blood count). From cycle 2 onwards pre-cycle bloods should be performed within 2 days of treatment. For patients on anti-coagulant therapy, appropriate clotting factors should be tested at each chemotherapy visit.
- Biochemistry including U&E, LFT, magnesium and calculated or measured GFR. From cycle 2 onwards pre-cycle biochemistry should be performed within 2 days of treatment
- QoL questionnaires when required - EQ-5D and EORTC QLQ-C30 and CR29 (at 3 and 6 months post randomisation)

If a patient stops their allocated treatment early or if the patient experiences treatment delays the BALLAD UK follow-up visits will still be due as per the protocol schedule i.e. timed relative to date of randomisation. This is the required procedure even if the patient has experienced treatment delays and is still receiving chemotherapy treatment.

4.1.3 Evaluations for patients on observation only: From randomisation to 6 months

Patients who are randomised to observation will only have a visit at 3 and 6 months post randomisation. At these visits the following will be performed:

- Haematology blood sample (full blood count).
- Biochemistry including U&E, LFT, magnesium and calculated or measured GFR

- QoL will be completed

The follow-up schedule (from 9 months post randomisation) will be the same as for those patients who are randomised to receive chemotherapy.

4.1.4 Follow up Evaluations

Patients will be followed up 9 months post randomisation and 12 months post randomisation. After that they will have visits on a six monthly basis until 3 years post randomisation and will then have annual visits for up to 7 years post randomisation.

Follow-up CT Scanning

CT Chest Abdomen and Pelvis will be performed at approximately 12, 24 and 36 months post randomisation. (Contrast enhanced CT Chest, abdomen and pelvis is the preferred method of assessment but MRI abdomen and pelvis with non-contrast enhanced chest CT may be used instead where clinically indicated).

Additional CT scans may also be conducted as clinically indicated based on symptoms, clinical markers or to accommodate sites usual scanning regimen.

CT scans performed within 42 days of the follow-up visits may be used for disease assessment. If the time interval from CT to follow up visit is more than 42 days a new CT scan should be performed.

If a patient has reached the primary endpoint of the trial and has a recurrence or a new primary tumour (CT confirmed) then further protocol mandated CT scans are no longer required. Any post recurrence CT scans should be performed as per local practice at the discretion of the investigator. The results of any further scans should be recorded in the appropriate section of the Case Report Form (CRF) unless the patient has commenced further palliative systemic therapy.

Follow-up Quality of Life Assessments

Please see the schedule of assessment for collection time-points during treatment (baseline, 3 and 6 months post randomisation).

EORTC QLQ-C30 and CR29 will be completed at 9, 12, 18 and 24 months post randomisation for all arms of the trial.

The EQ-5D will be completed at 9, 12, 18, 24, 30, 36, 48, 60 72 and 84 months post randomisation for all arms of the trial.

For patients that have a recurrence or have a new primary tumour the quality of life questionnaires should continue to be completed as per schedule of assessments provided it is deemed appropriate to ask the patient to do so.

Resource use for health economic assessment

Resource use data collection for the health economic assessment will be limited to health service resource use in the secondary care setting. Data (hospital inpatient, outpatient and day cases, cytotoxic drug use at relapse) will be collected on the treatment and follow-up forms.

4.2 Translational Research

Funding has been secured to support the collection of FFPE blocks and bloods for patients on the BALLAD UK trial. The aim of collecting this material is to establish a large biobank of SBA tissue and blood with complete and comprehensive trial quality follow-up data which will act as the foundation for many future collaborative research projects and for combined projects with other funded tissue collections. Expected research projects arising will include definition of new prognostic markers in this group of patients and definition of pharmacogenetic markers of 5-FU/capecitabine and oxaliplatin toxicity, particularly high grade diarrhoea and neurotoxicity.

This is a hugely important and integral part of the BALLAD UK trial that will significantly enhance the potential impact and clinical applicability of the results of the main body of the trial. We are therefore keen that all researchers contribute as much as possible to this part of the trial and encourage their patients to give their consent to allow this to take place.

Tumour Specimens:

We plan to collect the paraffin embedded tumour tissue which will have been obtained at surgical resection of patient's primary tumour prior to entry into BALLAD UK.

Blood samples:

We will collect blood samples – a 5ml serum sample and 2 x 9ml EDTA samples (for DNA) from each patient who consents to this. **If possible we would prefer it if these bloods could be taken prior to starting the adjuvant therapy**. However, it would still be useful to receive these bloods taken at any point during the treatment or follow-up period and there is still very useful translational research that we can carry out on these samples whatever the time-point at which they are collected. Therefore please do send samples from any patient who consents to give their blood for this research (and are not known to have had disease progression at the time of sampling).

Sample collection, storage and processing:

Further detailed instructions for the processing, labelling, handling storage and shipment of these specimens will be provided by in a separate BALLAD laboratory manual.

Proposals for specific translational research projects utilising the material will be considered by the Trial Management Group and presented to the Umbrella Trial Steering Committee for approval.

4.3 Trial Endpoints

4.3.1 Primary Endpoints

Disease free survival is the primary end point for the trial. This is defined at time from randomisation to the first occurrence of the following events:

- Disease relapse (confirmed by imaging)
- Incidence of a new primary (confirmed by imaging and histology/cytology)
- Death from any cause

Patients who experience none of these events are censored at the last date known to be alive.

4.3.2 Secondary Endpoints

Overall survival: The patient's survival status is determined at each follow-up visit. After the mandated clinic visits survival status data will come from responsible cancer centres, cancer registries and national databases and include long-term passive follow-up data such as that collected through collaboration with the National Cancer Intelligence Network and the Office of National Statistics in the U.K.

Toxicity of chemotherapy: Toxicity will be assessed using CTCAE version 4.0. Only toxicities that are at least grade 2 will be recorded on the CRF

Quality of life: This is assessed using the EORTC QLQ-C30, EORTC QLQ-CR29 v2.1 and EQ-5D scales as per the schedule indicated in section 4.1.5

Health Economics: Assess the cost-effectiveness of 24 weeks adjuvant chemotherapy in comparison to observation alone; and assess the cost-effectiveness of 24 weeks adjuvant 5-FU/Capecitabine monotherapy compared to 5-FU/Capecitabine plus Oxaliplatin. Outcomes will be reported as incremental cost per DFS and incremental cost per QALY.

Establishment of a central tissue bank for patients with SBA – further details on this tissue bank can be found in section 4.2, Translational Research.

Establishment of a central repository of clinic-pathological, epidemiological and molecular profiling data of patients being treated with SBA in this trial.

5 TREATMENTS

5.1 Treatment Arms

All drugs administered as part of the Group 1 & 2 randomisations are considered Investigational Medicinal Products (IMPs) for the purposes of this protocol (this includes folinic acid).

Group 1: Patients will be randomised between observation and chemotherapy. Those patients who draw the chemotherapy arm and who have consented to this can go on to be randomised into the group 2 question. This is to be encouraged as it will add significant value and improve efficiency of the trial.

Group 2: Patients will be randomised to receive therapy with a fluoropyrimidine regimen or combination therapy of fluoropyrimidine plus oxaliplatin. Investigators must specify the fluoropyrimidine regimen at the time of randomisation for each individual patient. Any accepted institutional standard IV 5-FU/Folinic Acid regimen or oral capecitabine regimen may be used. The combination regimen is specified as oxaliplatin delivered as part of a standard institutional fluoropyrimidine combination regimen. Use of other fluoropyrimidine +/- oxaliplatin regimens can be discussed with the CI or his approved representative through the Glasgow CRUK Clinical Trials Unit where eligibility of the regimen will be considered.

Treatment will continue for up to 24 weeks (or 26 weeks if this is the usual duration for an institution's approved fluoropyrimidine regimen) unless stopped early for one of the reasons outlined in section 5.10. Patients with difficulty swallowing can be switched from Capecitabine to 5-FU at any point during the trial as per investigators discretion.

Patients with DPD Deficiency

Reduced activity of DPD is one of the main causes of fluoropyrimidine-related toxicity, due to the lower capacity to degrade fluorouracil into the inactive metabolites, resulting in higher exposure of fluorouracil and cytotoxic metabolites. Most often, a DPD deficiency is the result of a deleterious single nucleotide polymorphism (SNP) in DPYD, altering the DPD enzyme activity. A DPD deficiency is classified as partial if there is remaining DPD activity (e.g. 25-50% of normal). Patients with complete DPD deficiency are excluded from this study, as will be certain patients who have compound heterozygosity.

Patients who are heterozygous carriers for any of the four variants below and who are to receive intravenous fluorouracil or oral capecitabine, should have their starting dose of fluorouracil (both loading doses and infusional doses) or capecitabine (either as monotherapy or in combination with oxaliplatin) reduced by 50%. These recommendations may be revised based on updated local/national guidance, and we recommend that all patients with partial DPD deficiency are discussed with the sponsor and Chief Investigator prior to agree their starting dose:

DPYD variant	**% of Fluorouracil or Capecitabine starting dose**
DPYD*2A (c.1905 + 1G>A; rs3918290)	50%
DPYD*13 (c.1679T>G; rs55886062)	50%
c.2846A>T (rs67376798)	50%

c.1236G>A/HapB3 (rs56038477)	50%

For patients established on treatment, who are experiencing no or clinically tolerable toxicity with fluorouracil, the dose may be cautiously escalated in subsequent cycles by 25% dose increments. Please contact the sponsor and Chief Investigator if further discussion on this issue is required.

5.2 Specific Drug Information

5.2.1 Fluorouracil

Fluorouracil is supplied as a clear, colourless or slightly yellow solution for injection. It is available as 25mg/ml and 50 mg/ml and either may be used in the trial, depending on standard supplies available at the trial site.

Please see the Summary of Product Characteristics (SmPC) for further detail.

5.2.2 Folinic Acid

Folinic Acid is available in a variety of salt forms and any brand or salt form of folinic acid may be used. However if a site chooses to switch brands during the trial, the Sponsor must be informed and sites are requested to contact CRUK Glasgow CTU. If L-Folinic Acid is used, the doses must be adjusted accordingly.

Please see SmPC for further detail.

5.2.3 Capecitabine

Capecitabine is supplied as film-coated tablets. The 150mg tablets are light peach film-coated tablet of biconvex, oblong shape. The 500mg tablets are peach film-coated tablet of biconvex, oblong shape.

Please see SmPC for further detail.

5.2.4 Oxaliplatin

Oxaliplatin is supplied as a powder for reconstitution for injection or as a solution for injection. It is available as 5mg/ml and either presentation may be used in the trial, depending on standard supplies available at the trial site.

Please see SmPC for further detail.

5.3 Dispensing, Accountability and Administration

Chemotherapy regimens will be administered as per institutional standard care and are the choice of the Principal Investigator (PI) at that site. The choice of regimen should be notified to CRUK Glasgow CTU at the time of randomisation. The suggestions below are for guidance and differences in standard practice can be permitted, e.g., doses, infusion times, infusion volumes – **these must be notified to**

the sponsor for approval at the time of initiation. The use of disposable infusion pumps and PiCC or other central lines for the delivery of the fluorouracil is permitted. The choice of regimens that will be used at the site can be discussed with the Chief Investigator (CI) or his approved representative through the Glasgow CRUK Clinical Trials Unit, at the time of initiation.

Chemotherapy doses may be recalculated every cycle during treatment if it is local practice to do so e.g. automatic updates by electronic prescribing systems. Where it is not local practice to recalculate every cycle the doses MUST be recalculated if the subject's weight changes by greater than or equal to 10% from baseline. It is not recommended that BSA is capped, but if it is local practice to cap BSA then this is acceptable as long as the sponsor is notified of this at the time of site opening.

Breaks, other than due to toxicity, are not recommended. However, if the patient needs a break for reasons other than toxicity; and the Investigator believes it to be in the patient's best interest, a break of up to 3 weeks maximum is permitted. Such 'treatment holidays' must be discussed with the CRUK Glasgow CTU for approval.

Treatment on day 1 may be administered up to 48 hours before or after the scheduled day 1 for all chemotherapy regimens for administrative reasons.

5.3.1 Examples of permitted Fluoropyrimidine Regimens

5.3.1.1 Intravenous Bolus/Infusional Fluoropyrimidine Regimens

Folinic Acid 350mg IV in 250ml Glucose 5% over 2 hours D1
5-Fluorouracil 400mg/m^2 IV in 100ml Sodium Chloride 0.9% over 10 minutes D1 (or as an IV bolus)
5-Fluorouracil 2400mg/m^2 IV. in 1000ml Sodium Chloride 0.9% (or via central/PICC line) over 46 or 48 hours D1
Repeat every **TWO** weeks.

For patients with **partial DPD deficiency**:
Folinic Acid 350mg IV in 250ml Glucose 5% over 2 hours D1
5-Fluorouracil 200mg/m^2 IV in 100ml Sodium Chloride 0.9% over 10 minutes D1 (or as an IV bolus)
5-Fluorouracil 1200mg/m^2 IV in 1000ml Sodium Chloride 0.9% (or via central/PICC line) over 46 or 48 hours D1
Repeat every **TWO** weeks.

5.3.1.2 Oral Fluoropyrimidine Regimens

Capecitabine 1250mg/m^2 PO twice daily for 14 days D1
Repeat every **THREE** weeks.

For patients with **partial DPD deficiency**:

Capecitabine 625mg/m^2 PO twice daily for 14 days D1

Repeat every **THREE** weeks.

5.3.2 Examples of permitted Combination Fluoropyrimidine Regimens

5.3.2.1 Intravenous Combination Fluoropyrimidine Regimens

Oxaliplatin 85mg/m^2 IV in Glucose 5% (volume as determined by dose) over 2 hours D1

Folinic Acid 350mg IV in 250ml Glucose 5% over 2 hours concurrently with Oxaliplatin D1.

Fluorouracil 400mg/m^2 IV in 100ml Sodium Chloride 0.9% over 10 minutes (or as an IV bolus) D1

Fluorouracil 2400mg/m^2 IV in 1000ml Sodium Chloride 0.9% (or via central/PICC line) over 46 or 48 hours D1

Repeat every **TWO** weeks.

For patients with **partial DPD deficiency**:

Oxaliplatin 85mg/m^2 IV in Glucose 5% (volume as determined by dose) over 2 hours D1

Folinic Acid 350mg IV in 250ml Glucose 5% over 2 hours concurrently with Oxaliplatin D1.

Fluorouracil 200mg/m^2 IV in 100ml Sodium Chloride 0.9% over 10 minutes (or as an IV bolus) D1

Fluorouracil 1200mg/m^2 IV in 1000ml Sodium Chloride 0.9% (or via central/PICC line) over 46 or 48 hours D1

Repeat every **TWO** weeks.

5.3.2.2 Oral Combination Fluoropyrimidine Regimens

Oxaliplatin 130mg/m^2 IV in Glucose 5% (volume as determined by dose) over 2 hours Day 1

Capecitabine 1000mg/m^2 PO twice daily for 14 days starting on day 1

Repeat every **THREE** weeks.

For patients with **partial DPD deficiency**:

Oxaliplatin 130mg/m^2 IV in Glucose 5% (volume as determined by dose) over 2 hours Day 1

Capecitabine 500mg/m^2 PO twice daily for 14 days starting on day 1

Repeat every **THREE** weeks.

5.4 Trial Drug Supplies

All trial drugs for use in the trial should be taken from usual pharmacy stock; there is no provision for funding, reimbursement or discounted stock. Shelf stock will not require IMP labelling but all IMP being dispensed to patients must be labelled at site, at the time of dispensing, in accordance with all

applicable regulatory requirements. See separate IMP Management Document for further detail on labelling requirements.

5.5 IMP Preparation and Administration

All trial drugs for use in the trial will be prepared and administered as per accepted institutional standard. Dose banding is permitted where it is local practice to do and this must be notified to the Sponsor at the time of initiation.

5.6 Supportive Medication

Pre-medication as prophylaxis for nausea and vomiting is recommended as per local protocols. In addition, for individual patients where local vein pain is a problem during infusion, then protocols, such as increasing infusion time, piggy-backing chemotherapy with glucose infusions etc. or use of a central venous device can be instigated.

Antidiarrhoeal therapy and skin emollients may be administered as per local protocol for managing capecitabine toxicities.

5.7 Use of Calcium and Magnesium Supplements

The use of calcium or magnesium supplements is prohibited during oxaliplatin administration when given to prevent or treat acute neuropathy as this has been shown to be ineffective. However, magnesium, calcium or phosphate supplementation either orally or intravenously for patients low in these minerals as replacement therapy is permitted.

5.8 Concomitant Therapies

Surgery

Surgery is allowed during the trial for adhesive or other obstruction, intercurrent other disease or for any other clinically appropriate reason. Continuation of adjuvant chemotherapy after a break where appropriate may be permitted following discussion with the CI or his approved representative through the Glasgow CRUK Clinical Trials Unit.

Radiotherapy

Radiotherapy is not permitted during the trial.

5.9 Prohibited Medications and Potential Drug Interactions

5.9.1 Drug Interactions

The drugs listed below may interact with some of the IMPs given as part of this trial. These drugs are not considered to be a recommended standard treatment for this patient group but there may be instances where patients receive these treatments concomitantly. If this is the case, then caution should be taken as indicated below. These medications are not considered to be Non-Investigational Medicinal Products (NIMPs) for this trial.

This list is not intended to be comprehensive, and local practice and guidelines and SmPCs should be followed for management of all other drugs.

Warfarin and Direct Oral Anti-Coagulants (DOACs)

It is recommended that patients DO NOT receive concomitant capecitabine and warfarin as the disturbance in warfarin metabolism during capecitabine treatment is unpredictable and difficult to manage. Wherever possible the recommendation is to treat the patient with low molecular weight heparin instead of warfarin. If the Local Investigator feels there is no alternative to giving capecitabine and warfarin concurrently then these patients MUST have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin and phenprocoumon. The use of DOACs alongside chemotherapy is unproven and will be established by currently ongoing clinical trials, and so use of DOACs with chemotherapy in this trial is not recommended.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine or 5-FU and phenytoin. Patients taking phenytoin concomitantly with capecitabine or 5-FU should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Allopurinol

Interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided. If viewed by the investigator as necessary, then this should be discussed with the CRUK Glasgow CTU.

Antivirals

Brivudine and sorivudine MUST NOT be prescribed with capecitabine or 5-FU as they may produce a life-threatening interaction. These drugs are not licensed for use in the UK but may be prescribed in other countries. There must be at least a 4-week waiting period between end of treatment with these drugs and start of capecitabine or 5-FU therapy. Treatment can be started 24 hours after the last dose of capecitabine.

Live Vaccines

Vaccination with a live vaccine should be avoided in patients in patients receiving 5-FU or oxaliplatin due to the potential for serious or fatal infections. Vaccination with the COVID-19 vaccine is permitted

as long as government guidelines are followed and a live attenuated vaccine is NOT given [Please note, although the AstraZeneca/ Oxford Covid-19 vaccine contains a live adenovirus vector, it is impossible for the vaccine to replicate or cause disease in humans and is therefore considered safe in immunosuppressed patients]. Please check with Sponsor for clarification if needed, prior to administration of any Covid-19 vaccine.

Photosensitivity

In patients treated with 5-FU, prolonged exposure to sunlight is not advisable because of the risk of photosensitivity.

Concomitant medicines known to prolong QT interval

Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored.

Concomitant medicines known to be associated with rhabdomyolysis

Rhabdomyolysis has been reported in patients treated with oxaliplatin, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, oxaliplatin treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicinal products associated with rhabdomyolysis are administered concomitantly with oxaliplatin.

5.10 Dose Modifications

Dose delay and dose reduction of all IMPs will be carried out as per institutional standard care (and SmPC for capecitabine). These can be discussed with the CI (or his approved representative) if desired.

5.10.1 Dose Modifications for Toxicity

Expected toxicities are detailed in appendix 3. Dose modifications for diarrhoea, haematological toxicity and neurotoxicity are as described below, after some general rules and observations about managing toxicity.

If any grade 1 toxicity occurs as a result of chemotherapy, then treatment will be continued, without interruption, at full dose. For all non-haematological treatment related toxicities ≥ grade 3, treatment should be withheld until recovery to ≤ grade 1 then restarted commencing as day one of the next cycle, if medically appropriate. Haematological toxicities should be treated as per section 5.10.2.

If patients take more than 4 weeks to recover from chemotherapy related toxicity they will receive no further protocol mandated treatment, but will still be followed up as per the BALLAD UK protocol.

Wherever possible, Oxaliplatin should be dose reduced (at investigator's discretion) rather than discontinued and can be given over a longer period of time. In the situation where Oxaliplatin is discontinued due to toxicity, adjuvant treatment can continue with 5-FU or Capecitabine alone if deemed appropriate by the local investigator. In this case, the dose per m^2 of the single agent fluoropyrimidine can be increased to the standard single agent dose of that drug as per local practice at the discretion of the Investigator. Patients will still be considered to be on BALLAD UK protocol treatment and will be followed up as per the BALLAD UK protocol.

Crossover from Capecitabine to IV 5-FU and vice-versa is permitted if this is required to control toxicity. This crossover should be managed as per institutional standards.

For toxicities or combinations of toxicities not specifically covered in detail in this protocol, doses of chemotherapy can be reduced at the discretion of the Investigator as per local practice.

Any dose modifications must be recorded on the CRF and documented in the patient notes.

5.10.2 Dose Modification for Haematological Toxicity

The following dose modifications are provided <u>as a guideline</u> in the event of a haematological toxicity, however Investigators are permitted to follow their local practice for the management of haematological toxicity, with all dose modifications fully documented in the patient's medical records and CRFs.

For patients on 3 weekly chemotherapy:

Neutrophils		**Platelets**	**Dose Modification**
≥1.5 x 10^9/l	and	≥75 x10^9/l	Treat with full dose on time
<1.5 x 10^9/l	and/or	<75 x 10^9/l	Delay treatment until neutrophils and platelets are above these limits and dose reduce as below
Fluoropyrimidine Regimens Capecitabine should be modified as per SmPC in relation to grading of toxicities. **Combination Fluoropyrimidine Regimens** **Capecitabine and Oxaliplatin treatment** If > 1 delay, or 1 delay of ≥ 2 weeks occurs, reduce capecitabine and oxaliplatin doses by 25% and continue at the lower dose for subsequent cycles unless further toxicity occurs. If further delay(s) for myelotoxicity occur despite a 25% dose reduction, further dose reductions may be made, at the discretion of the local Investigator. Capecitabine dose should be further modified as per SmPC in relation to grading of toxicities **<u>Following first cycle of chemotherapy</u>**			

If on the day the second, or subsequent cycle, is due neutrophils are between 1.0 and 1.5 and/or platelets are between 50 and 75, delay until recovery and then reduce doses for subsequent courses by 25%

If on the day the second, or subsequent cycle, is due neutrophils are between 0.5 and 1.0 and/or platelets are between 25 and 50, delay until recovery and then reduce doses for subsequent courses by 50%. A 25% dose reduction with G-CSF would be an acceptable alternative.

If on the day the second, or subsequent cycle, is due neutrophils are <0.5 and/or platelets <25, investigators should discontinue treatment

If delay ≥ 4 weeks patient will no longer be considered to be on protocol treatment, however the patient **will** continue to be followed up as per protocol.

G-CSF management of neutropenia will be at the discretion of the local Investigator.

For patients on 2 weekly chemotherapy:

Neutrophils		**Platelets**	**Dose Modification**
≥1.0 x 10^9/l	and	≥75 x10^9/l	Treat with full dose on time
<1.0 x 10^9/l	and/or	<75 x 10^9/l	Delay treatment until neutrophils and platelets are above these limits and dose reduce as below

Fluoropyrimidine Regimens

5-FU dose should be modified as per standard local policy.

Combination Fluoropyrimidine Regimens

5-FU and Oxaliplatin treatment

If > 1 delay, or 1 delay of ≥ 2 weeks occurs, maintain oxaliplatin and infusional 5-FU doses , but omit bolus 5-FU and continue without bolus 5-FU for subsequent doses.

If further delay(s) for myelotoxicity occur despite omitting bolus 5-FU, reduce the oxaliplatin and infusional 5-FU doses by 25%. Further dose reductions can be made at the discretion of the local Investigator.

Following first cycle of chemotherapy

If on the day the second, or subsequent cycle, is due neutrophils <1.0 and/or platelets are between 50 and 75,, reduce doses for subsequent courses by 25% (and omit bolus 5-FU from OxMdG regimen).

If on the day the second, or subsequent cycle, is due neutrophils ≤0.5 and/or platelets <50, Investigators may at their discretion reduce doses for subsequent courses by 50% (and omit bolus 5-FU from OxMdG regimen). A 25% dose reduction with G-CSF would be an acceptable alternative.

If delay ≥ 4 weeks patient will no longer be considered to be on protocol treatment, however the patient **will** continue to be followed up as per protocol.

G-CSF management of neutropenia will be at the discretion of the local Investigator.

Use of granulocyte colony stimulating factor (G-CSF) is permitted at the discretion of the investigator in this potentially curative situation and in keeping with ASCO or other appropriate institutional or

national guidelines. As with all concomitant medication, its use (including dosage, duration and indication) should be accurately documented.

5.10.3 Dose Modification for Neurosensory Toxicity

Neurosensory toxicity with these regimens is known to be a consequence of the oxaliplatin. Therefore reduction in this drug is the most important adjustment to make. The table below gives recommendations but is not meant to be prescriptive and dose adjustments according to local protocol may be followed as long as the dose given is carefully annotated in the CRF.

Regimen	Grade 1, or 2 (if Grade 2 persisting ≤7 days)	Grade 2 persisting >7 days	Grade 3	Grade 4
5-FU and Oxaliplatin	Full dose oxaliplatin	Reduce oxaliplatin dose by 25%	Discontinue oxaliplatin	Discontinue oxaliplatin
Capecitabine and Oxaliplatin	Full dose oxaliplatin	Reduce oxaliplatin dose by 25%	Discontinue oxaliplatin	Discontinue oxaliplatin

Acute dysasthesia of the larynx may be mitigated by slowing the rate of infusion of oxaliplatin.

If repeat events of neurosensory toxicity occur; local practice should be followed in terms of any dose reductions applied, with the management of the toxicities being fully documented in the patient's medical records.

5.10.4 Dose Modification for Diarrhoea

Diarrhoea with these regimens is a known consequence of 5-FU and capecitabine. Therefore a dose reduction in these drugs is the most important adjustment to make. The table below gives recommendations and dose adjustments according to local protocol may be followed as long as the dose given is carefully annotated in the CRF.

	Grade 2	Grade 3	Grade 4
1st occurrence	Withhold 5-FU/capecitabine treatment until recovered to grade 0-1. Restart at full dose	Withhold 5-FU/capecitabine treatment until recovered to grade 0-1. Restart with a 25% dose reduction	Discontinue all chemotherapy **or** if physician deems it in

			patient's best interest interrupt until resolved to grade 0-1 and restart with 50% 5-FU/capecitabine
2nd occurrence	Withhold 5-FU/capecitabine treatment until recovered to grade 0-1. Restart at 75% dose	Withhold 5-FU/capecitabine treatment until recovered to grade 0-1. Restart at 50% dose	
3rd occurrence	Withhold 5-FU/capecitabine treatment until recovered to grade 0-1. Restart at 50% dose	Discontinue all chemotherapy	
4th occurrence	Discontinue of all chemotherapy		

If dose reduction of capecitabine or 5-FU does not result in improved tolerance then consideration should be given to reduction of oxaliplatin dose to 100 mg/m^2 on Capecitabine/Oxaliplatin regimen or 75 mg/m^2 on 5-FU/Oxaliplatin regimen.

5.10.5 Dose Modifications for other reasons

Respiratory Toxicity

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.

Stomatitis

Routine mouthcare is recommended. If mouth ulcers occur despite this, dose reduce capecitabine or 5-FU as per table for diarrhoea.

Hand-foot Syndrome (HFS)

Treat symptomatically – e.g. Pyridoxine 50 mgs tds by mouth can be used as per Investigator discretion; or a topical corticosteroid may help. If HFS is still a problem, reduce the dose of capecitabine or 5-FU as per table for diarrhoea.

Allergic Reactions to Oxaliplatin

Some patients (approximately 15%) develop acute hypersensitivity to oxaliplatin. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity. This rarely develops to full-blown anaphylaxis, even with repeated treatment. If hypersensitivity does occur a desensitisation protocol as per local practice can be followed and the dose of subsequent cycles be given over a longer time period.

If severe hypersensitivity occurs, discontinue the infusion and treat with IV corticosteroid and antihistamine, as per local practice. After full recovery, the patient may continue with folinic acid and 5-FU or capecitabine.

Oxaliplatin induced laryngeal spasm

If a patient develops laryngeal spasm with no other symptoms of allergic reaction then treatment should be as per investigators discretion and patient should continue on study treatment.

Abnormal Liver Function Tests

In cases of abnormal liver function test results or portal hypertension, which does not obviously result from liver metastases, very rare cases of drug induced hepatic vascular disorders should be considered. Incidences of abnormal liver function tests thought to be attributable to oxaliplatin should be managed as per local practice and documented in the CRF.

Specific Management of Patients taking Capecitabine

Patients allocated Capecitabine must be properly educated in the management of their home-based oral chemotherapy and need to be given rigorous advice with respect to contacting the hospital as soon as toxicities ensue.

Patients may often be prepared to experience toxicities and may not easily accept the idea of interrupting their treatment for fear this may decrease efficacy. Patients should be re-assured that protocol compliant dose modifications will not compromise the efficacy of their treatment, and must be given clear instructions on when to discontinue capecitabine and who to contact (local Investigator/Research Nurse) at the onset of key toxicities such as nausea/vomiting and diarrhoea.

Cardiotoxicity has been associated with fluoropyrimidine therapy and these adverse reactions may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris (see Capecitabine SmPC for further information). Incidences of cardiotoxicity arising from capecitabine treatment should be managed as per standard local practice and documented in the CRF.

5.11 Participation in Concurrent Clinical Trials

In general patients should not participate simultaneously in more than one trial, with the following exceptions:-

- Patients will be permitted to take part in observational research at any time whilst participating in this trial
- Patients who have attained the primary trial end-point and are no longer receiving the trial intervention.
- Patients who have progressed can enter a trial for recurrent or metastatic disease

If an exception is considered outwith the above general criteria the PI seeking the exception must seek approval from the CI and Trial Management Group prior to enrolling the patient in the other trial. It is imperative that the Sponsors of both studies also approve co-enrolment within their trial.

5.12 Duration of Trial Participation

5.12.1 Duration of Trial Treatment

Trial treatment will continue for up to 24 weeks (or 26 weeks for certain permitted regimens).

5.12.2 Duration of Trial Follow Up

Patients will be followed up for up to 7 years post randomisation

6 PHARMACOVIGILANCE

Safety assessments will be performed in line with guidance specified in The Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments to it. The following definitions and reporting requirements apply to BALLAD UK only.

6.1 Definitions

These definitions apply to all trial participants from the first dose of trial medication.

6.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

6.1.2 Adverse Reaction (AR)

An adverse reaction (AR) is any untoward and unintended occurrence in a subject to whom a medicinal product has been administered, which is thought to be caused by or related to that product.

6.1.3 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any of the following, whether or not considered related to the trial treatment.

- Results in death
- Life-threatening (i.e. at the time of the event)*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is considered medically significant by the Investigator***

*Life threatening means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

**Requires in-patient hospitalisation should be defined as a hospital admission required for treatment of an adverse event.

***Considered medically significant by the Investigator, are events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.1.4 Serious Adverse Reaction (SAR)

A serious adverse reaction (SAR) is a SAE that may be related to trial treatment. The assessment of "relatedness" is primarily the responsibility of the PI at site or agreed designee. SAEs will be considered related if the SAE is documented as possibly, probably or definitely related to protocol treatment. The assessment of relatedness is made using the following:

Relationship	Description
Unrelated	There is no evidence of any causal relationship.
Possible	There is some evidence to suggest a causal relationship (e, g. the event occurs within a reasonable time after administration of the trial medication). However the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors in unlikely.

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

6.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Relation (SUSAR) is any suspected SAR that is unexpected. Unexpected is any reaction that is not a known reaction listed in the section of the current regulatory approved SmPCs, which are acting as the reference safety information (RSI) for the trial treatments. Please note the version of the RSI that has regulatory approval may not be the most up-to-date version of the SmPC that has been provided to Investigators for advice on the clinical management of their trial patients.

6.2 Detecting, Recording and Reporting of Adverse Events

6.2.1 Detection of Adverse Events

Participants will be asked at each trial visit about the occurrence of AEs since the last visit.
AEs will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and the trial protocol.
AEs must be recorded as they are reported, whether spontaneously volunteered or in response to questioning about wellbeing at trial visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. All adverse events must be documented in the patient's medical records and in the CRF as required.

6.2.2 Recording of Adverse Events

Full details of AEs including the nature of the event, start and stop dates, severity, relationship to trial drug and outcome will be recorded in the patient's medical records. However, only AEs that are grade 2 or above require entry on the trial CRF. All AEs must be followed until they resolve or return to the baseline value, or if they do not resolve, for at least 30 days after discontinuation of trial medication or until they are confirmed as likely to never resolve. Perceived lack of efficacy is not an AE. An exacerbation of a pre-existing condition is an AE.

6.2.3 Assessment of Adverse Events

All AEs and toxicities must be graded according to the NCI-CTCAE Version 4. These criteria can be accessed via the National Cancer Institute Website.
AEs must be assessed for seriousness, causality and severity. This assessment is the responsibility of the PI (or designee).

6.3 Reporting of a Serious Adverse Event

SAEs must be reported by email or fax to the Pharmacovigilance Office, CRUK Glasgow CTU immediately and under no circumstances should this exceed 24 hours following first awareness of the event by the Investigator or site staff:

Pharmacovigilance Office, CRUK Glasgow CTU

Fax no: +44 (0) 141 232 2157

Tel no: +44 (0) 141 232 2068 or 211 3567/3968/0203/0352

Email: mvls-ctu-pv@glasgow.ac.uk

For guidance on submitting and completing initial and follow up SAE report forms please refer to the SAE Completion Guidelines, which will be provided by the Pharmacovigilance (PV) Office, CRUK Glasgow CTU.

All initial SAE reports will have a SAE reference number generated for the event and will be acknowledged by the Pharmacovigilance Office. If no acknowledgement is received within 48 hours sites are required to contact the Pharmacovigilance Office to check the report has been successfully submitted and received.

When the causality of a SAE is assessed by Investigators to be unrelated to the IMPs, Investigators must include in the SAE report what the SAE is related to i.e. whether the SAE is assessed as being related the disease under investigation, a concurrent illness or concomitant medication, or another possible cause.

When no causality is provided by an Investigator the SAE will, for the purposes of regulatory reporting, be treated as related to the IMP until a causality assessment is provided by the Investigator.

If a SAE is the result of a protocol related procedure this must be clearly explained in the SAE report.

The Chief Investigator (CI) will be notified by e-mail of all SAEs received. . SAEs must be reported locally by the Investigator at each site in accordance with the local practice at their site (i.e. Datix or R&D Office).

A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE is a potential SUSAR then follow up information must be

provided quickly and in the timeframe requested by the CRUK Glasgow CTU and CI. Information in addition to what is recorded in the SAE report form may be required to submit a SUSAR report to the Regulatory Authority.

All follow-up information for SAEs that are not SUSARs, also requires to be reported promptly, and follow up reports must be submitted until all SAEs listed on the initial SAE report resolve. A follow-up report must be submitted if additional SAEs listed on the initial SAE report resolve, or it is confirmed that they will never resolve. A follow-up report should also be submitted if additional SAEs occur or new information becomes available about previously reported SAEs.

Any event that meets the criteria for a SAE (including events that the Investigator thinks are medically significant but maybe do not require hospitalisation or are not fatal etc.) that occurs after 30 days post treatment is also required to be reported if the Investigator thinks the SAE is related to protocol treatment and is medically important. Such SAEs must be reported to the Pharmacovigilance office without undue delay and within 24 hours of first knowledge of the event.

For any questions relating to SAE reporting, please contact the PV team, contact details are provided below and at the front of the protocol and in the SAE Completion Guidelines.

Pharmacovigilance Office, CRUK Glasgow CTU

Fax no: +44 (0) 141 232 2157

Tel no: +44 (0) 141 232 2068 or 211 3567/3968/0203/0352

Email: mvls-ctu-pv@glasgow.ac.uk

6.4 When SAEs are not required to be Reported

SAEs that occur after consent and randomisation but prior to any trial treatment do not require to be reported.

In addition, the following events also do not require to be reported as SAEs:

- SAEs that are unrelated to the trial treatment
- Hospitalisation or death due to disease progression if trial treatment has ended
- Hospitalisation for planned investigations
- Hospitalisation for trial drug administration, palliative care, terminal care or elective surgery

6.5 Reporting of a SUSAR

CRUK Glasgow CTU on behalf of the Sponsor is responsible for the expedited reporting of all SUSARs to the required regulatory authority, Research Ethics Committee (REC), Investigators at trial sites and the trial Sponsor.

- Fatal or life threatening SUSARs will be reported within 7 days of the CRUK Glasgow CTU receiving the first notification of the unexpected event. Any additional information will be reported within eight days of sending the initial report.
- All other SUSARs will be reported within 15 days of the CRUK Glasgow CTU receiving the first notification of the unexpected event.

6.6 Pregnancy

Pregnancy occurring in a participant in the trial or the partner of a trial participant, while not considered an AE or SAE requires to be monitored and followed-up.

The Investigator must collect pregnancy information for female trial subjects or the female partners of trial subjects. This includes subjects who become pregnant whilst receiving trial drugs or for 12 months post trial treatment.

Any pregnancy occurring in a female subject or female partner of a male subject, while participating in the trial, must be reported by the Investigator (or designee) to Pharmacovigilance using the Pregnancy Notification Form (PNF) within 24 hours of the Investigator first becoming aware of the pregnancy. Pharmacovigilance will track the pregnancy until confinement. Pharmacovigilance will also request an anticipated delivery date. However, the Investigator is required to update and submit the PNF immediately with the outcome of delivery or if there is a change in the subject's condition such as miscarriage or termination or if new relevant information becomes available concerning the child. The updated PNF must be emailed (mvls-ctu-pv@glasgow.ac.uk) or faxed to the PV office (+ 44 (0)141 232 2157) as soon as the new information becomes available. Any pregnancies which result in a congenital anomaly or birth defect will require to be reported by the Investigator as a SAE. The Pharmacovigilance department will assist with providing guidance on reporting pregnancy outcomes as SAEs. SAEs that are the result of a birth defect are likely to be reported as SUSARs. Additionally, any defects or health concerns with the infant that become known post-delivery, must also be reported by the Investigator by submitting an updated PNF. Development Safety Update Reports

6.7 Development Safety Update Reports

The Development Safety Update Reports (DSURs) will be prepared for the BALLAD trial rather than by trial drug. The reports will be written by the CI and CRUK Glasgow CTU on behalf of the Sponsor. DSURs will be submitted to the Regulatory Authority, REC, U.K. and trial Sponsor within 60 days of the anniversary of obtaining the UK Clinical Trial Authorisation by the CRUK Glasgow CTU.

6.8 Reference Safety Information

The contents of Section 4.8 Undesirable Effects in the reference SmPCs identified by the Sponsor for Capecitabine, 5-Fluorouracil, Folinic acid and Oxaliplatin will act as the Reference Safety Information (RSI) for the trial. The Sponsor is responsible for identifying and informing the CRUK Glasgow CTU of updates to the RSI. The SmPCs with current regulatory approval for the trial will be used to assess SAE reports to identify SUSARs. The CI, Pharmacovigilance and the Sponsor will decide if updates to RSI will be implemented or if the RSI is to remain unchanged. Any update to the RSI that includes the addition of new expected reactions, will not be implemented until regulatory approval has been received for the update and the new DSUR reporting period has started.

The Sponsor is responsible for identifying and informing the CRUK Glasgow CTU of updates to the reference SmPCs. Investigators will be supplied with SmPCs and updated SmPCs when the Sponsor and/or CI conclude the update will assist with the clinical management of trial patients.

When updated SmPCs are circulated to Investigators for the Clinical Management of their trial patients a *front sheet* document will also be provided. The front sheet will record what is to be referred to by Investigators for clinical management and why the updated SmPC is being circulated.

6.9 COVID-19 vaccination and Safety Reporting

Where a deployed COVID-19 vaccine is suspected to be involved in the onset of a reported event it should be recorded as a concomitant medication. A causal relationship between the vaccine and the event, including potential drug interactions should be assigned by the reporting investigator.

If a reported event is suspected to be due to a deployed COVID-19 vaccine alone reporting investigators should ensure that standard Yellow Card reporting procedures are followed.

7 STATISTICS AND DATA ANALYSIS

7.1 Trial Design

The rare nature of the tumour means that the GLOBAL BALLAD collaboration is not designed to provide the level of evidence usually required from a stand-alone clinical trial. Instead the approach taken combines the frequentist approach of a randomised phase II screening trial with a Bayesian approach to combining and summarising evidence.

The sample size to answer each of the two trial questions (Adjuvant question/Oxaliplatin question) is derived from a conventional phase II screening design with 90% (or 80% depending on accrual) power to detect a difference in disease-free survival between the trial arms at the 20% 1-sided level of statistical significance. If the result from this trial is statistically significant at the 1-sided 20% level, the following will be done:

(i) The estimate of the hazard ratio for DFS obtained from the trial will be combined with prior beliefs obtained from clinicians. The posterior distribution derived from the trial data combined with the clinician prior will be used as the summary of the final trial results in terms of DFS. The clinician prior will be elicited from a group of experts using a graphical method with clear instructions and a standardised script, combined with examples and training exercises.

(ii) The observed hazard ratio for OS obtained from the trial will be combined with predicted OS for those patients who are still alive at the end of the trial. This prediction will be based on observed DFS and other patient characteristics/interim observations. This observed/predicted OS estimate will then be combined with prior beliefs obtained from clinicians, in the same way as for DFS, to obtain a posterior distribution for OS

7.2 Sample Size

These sample size estimates are for the GLOBAL-BALLAD collaboration.

It is estimated that survival rates and incidence of the various stage groups are:
Stage I (assumed incidence 10%): 55% 5 year overall survival.
Stage II (assumed incidence 45%): 45% 5 year overall survival.
Stage III (assumed incidence 45%): 30% 5 year overall survival.
R0 resected Stage IV (assumed incidence 0-5%): less than 30% 5 year overall survival.

Based on the experience in CRC, it is assumed that these 5 year OS rates are the same as 3 year DFS rates. We anticipate that there will be proportionately more patients with stage I-II SBA in group I and more stage III/IV SBA in group 2, and hence the 3 year DFS rate for group 1 patients will be approximately 45% and group 2 will be approximately 40%.

The hazard ratio (HR) for DFS observed in the QUASAR study was 0.78 and in the MOSAIC study was 0.77. This trial will target a HR of 0.775 for both the adjuvant chemotherapy and oxaliplatin questions, corresponding to a ~9% improvement in 3-year DFS. The number of DFS events required to detect this HR at the 20% 1-sided level of statistical significance is 287 (90% power) or 190 (80% power). The table below shows the number of patients required for both the adjuvant (Group 1) and Oxaliplatin (Group 2) questions assuming accrual over 5 years and 2 years of subsequent follow-up (incorporating one interim assessment for futility once half the events have been observed using Lan-DeMets spending function with an O'Brien-Fleming type boundary).

	80% Power	90% Power
Adjuvant Question	300	455
Oxaliplatin Question	280	425
Total	**580**	**880**

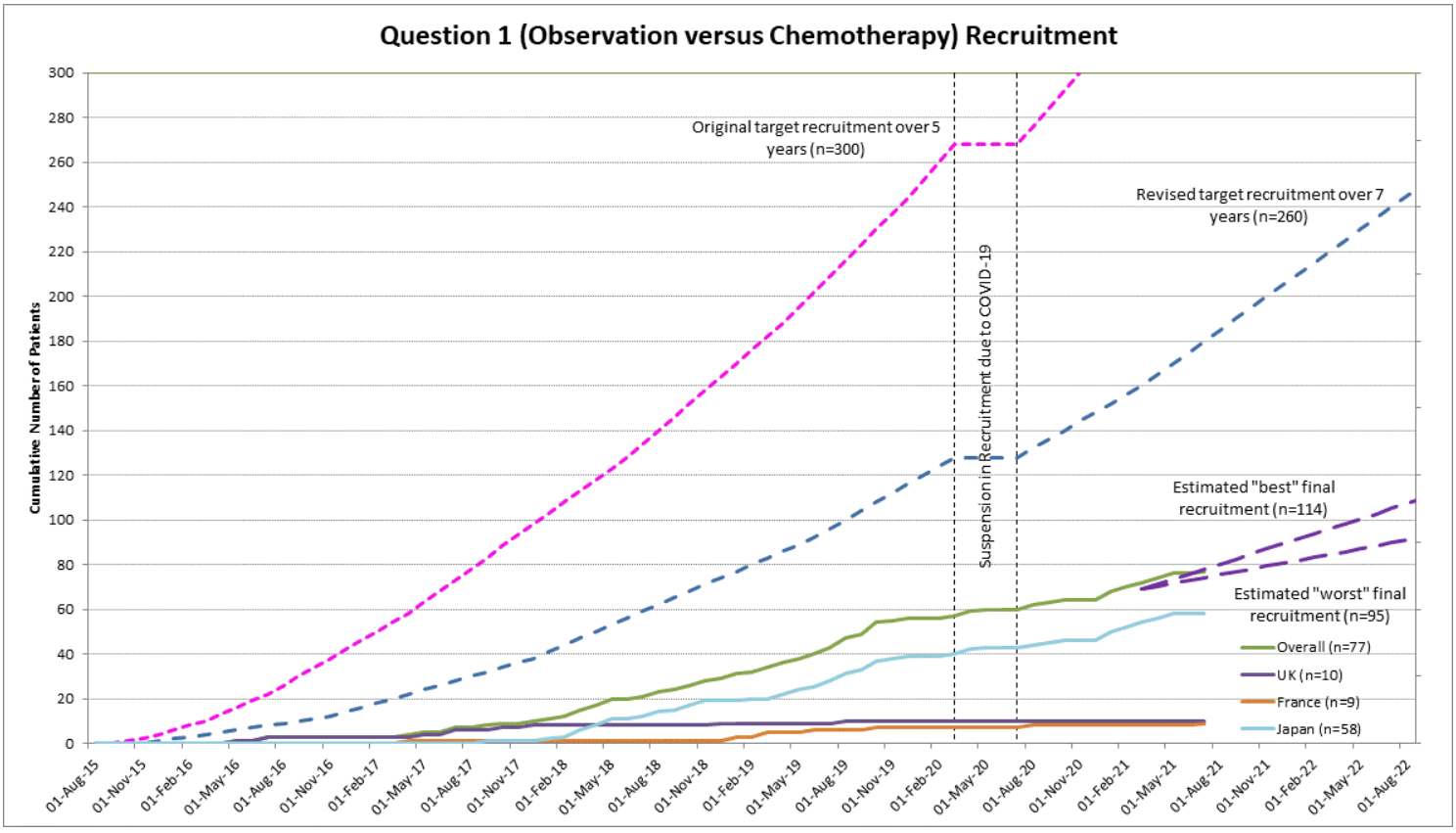
The total sample size requirement for both studies at 80% power is 3.9% of total incidence and for 90% power is 5.9%. Of course this total sample size requirement as a percentage of incidence would be further reduced depending on the proportion of patients who are randomised between the chemotherapy options in the adjuvant question (these calculations assume that no such patients are randomised).

The initial intention was to achieve 90% power for both questions, but consideration was given to the realities of recruitment meaning that only the sample size requirements for 80% power may have been realistic. Hence, the minimum sample size required was estimated to be 580 patients and the maximum was 880 patients (assuming no patients are randomised to the Oxaliplatin question from those recruited to the Adjuvant question).

The target recruitment for BALLAD UK was planned to be 120 patients.

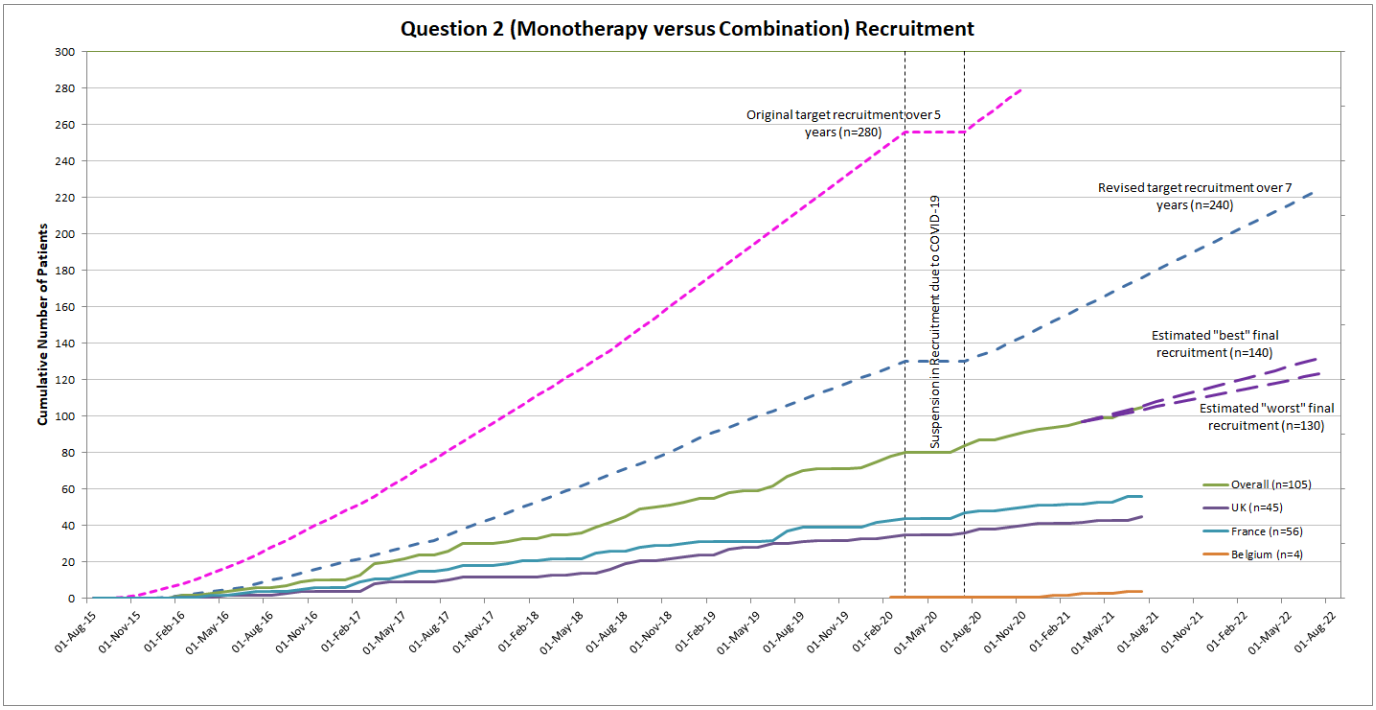
Recruitment to the study has been and continues to be challenging, however the study design is as permissive as is reasonable in this setting in terms of the power and significance level, so adjusting the sample size calculations is not appropriate. Calculations have been performed to estimate the final resultant power for both questions should the study continue at the rate observed since the study re-opened to recruitment following suspension due to the COVID-19 pandemic, and if recruitment were to increase to the highest observed rate of recruitment for that question.

Question 1: Observation versus Chemotherapy



The original recruitment target was 300 patients over 5 years which was revised to 260 patients over 7 years, both to obtain 190 events. The actual recruitment is estimated to be around 105 patients. Using the same constraints as the original design (alpha=0.2, HR=0.775, 45% survival at 3 years, 2 year follow-up) without a formal interim analysis for futility and adjusting the accrual to the actual observed accrual over the past 5 years, it is likely that around 68 events would be observed at the end of a 2 year follow-up, which would yield around 58% power.

Question 2: Monotherapy versus Combination



The original recruitment target was 280 patients over 5 years which was revised to 240 patients over 7 years, both to obtain 190 events. The actual recruitment is estimated to be around 135 patients. Using the same constraints as the original design (alpha=0.2, HR=0.775, 40% survival at 3 years, 2 year follow-up) without a formal interim analysis for futility and adjusting the accrual to the actual observed accrual over the past 5 years, it is likely that around 98 events would be observed at the end of a 2 year follow-up, which would yield around 66% power.

7.3 Analytical Plan

7.3.1 Primary Efficacy Analysis

The following approach will be taken for both trial questions (Adjuvant question and Oxaliplatin question). The primary frequentist analysis will be a conventional analysis of DFS using Cox regression techniques in the ITT population. Assuming this result is statistical significant at 20% 1-sided level of

statistical significance this result is then combined with the clinicians prior to determine a final posterior distribution.

Example: Assume the result of the trial was **just** statistically significant at 1-sided 20% level. The table below shows the 95% predictive intervals for DFS HR, based on trial data alone, a postulated clinician prior and the combined posterior distribution.

	Estimate of DFS hazard ratio	Lower limit of 95% predictive interval	Upper limit of 95% predictive interval
Trial data alone	0.88	0.65	1.18
Clinician prior	0.78	0.60	1.01
Combined posterior distribution	0.82	0.68	1.00

As can be seen when combined with the clinician prior, the 95% predictive interval excludes the possibility of any negative impact.

7.3.2 Secondary Efficacy Analysis

Survival: Although the trial is not powered for OS the results for both the Adjuvant and Oxaliplatin questions in terms of OS will be examined by:

(i) Estimating the observed OS HR from the trial.

(ii) Predicting OS from DFS and other patient characteristics/interim observations for those patients still alive at the end of the trial and using these estimated survival times combined with the actual observed times to re-estimate the OS HRs for the two trial questions (15)

(iii) Combining (ii) above with a clinician prior for the OS hazard ratio

7.3.3 Safety Analysis

The worst grade of CTCAE toxicity during the treatment period will be compared between the randomised arms for the Oxaliplatin question.

7.3.4 Quality of Life Analysis

The analysis of quality of life data will be based on AUC techniques (Qian W et al. Statistics in Medicine. 2000; 19: 2657-2674.)

7.3.5 Cost Effectiveness

The economic analysis will be undertaken from the perspective of the UK National Health Service (NHS), to assess the cost-effectiveness of adjuvant chemotherapy compared to observation only (Adjuvant question – Group 1) and 5-FU/FA or capecitabine compared to 5-FU/FA or capecitabine plus oxaliplatin (Oxaliplatin question – Group 2). Trial information on resource-use (i.e. treatment delivery, hospital inpatient/outpatient days etc.) will be combined with unit costs to estimate the mean cost per patient in each arm (including treatment costs, costs of managing adverse events and

costs of managing disease recurrence). Quality of life will be measured using the EQ-5D (16) to determine any difference over the course of the treatment period between trial arms, and beyond the treatment period up to 7 years follow-up. QoL estimates will be combined with DFS and OS and analysed as the area under the curve (AUC) to determine the mean difference in QALYs between the treatment arms, for both research questions. The analysis will be presented separately for the within trial and lifetime periods, in accordance with good practice guidelines and the NICE reference case (17-19).

A multivariate analysis of quality of life and costs, using the occurrence of adverse events and the stage of disease progression as explanatory variables, will be used to inform the lifetime cost-effectiveness model. The lifetime analysis will extrapolate the trial outcomes using a parametric survival model (e.g. weibull, log-logistic, gamma) based on fit to the observed data together with extensive sensitivity analysis following the approach recently recommended by the NICE Decision Support Unit (20,21). The model will be analysed probabilistically to characterise uncertainty in the parameters (22), and estimate confidence limits around the cost and effectiveness outcomes for each of the research questions.

7.4 Interim Analysis

The data from the GLOBAL BALLAD collaboration and BALLAD UK will be reviewed approximately annually by an independent Data Monitoring and Ethics Committee (see 12.6). If highly statistically significant differences are observed ($p<.0005$, one-sided) in favour of either adjuvant treatment or Oxaliplatin consideration will be given to stopping the corresponding aspect of the trial early.

It had been planned that for both study questions there would be a single formal assessment for futility once half the events have been observed (based on 90% power) using Lan-DeMets spending function with an O'Brien-Fleming type boundary, however due to the recruitment issues and the reduced sample sizes, these interim analyses will no longer take place; the DMEC will review the study data and advise if there are any potential issues regarding futility which require action.

After 2 years there will be a formal assessment by the Trials Steering Committee and DMC of whether the trial is meeting its accrual targets.

8 TRIAL CLOSURE/DEFINITION OF END OF TRIAL

For the purposes of the REC approval, the trial end date is deemed to be the date of the last data capture for the study and the data is clean.

8.1 End of Trial Notification

End of trial notification will be submitted to the competent authority and ethics committee within 90 days using the 'Declaration of the end of a clinical trial' form that can be found on the EudraCT website. However if the trial is terminated either (1) before the date for the conclusion of the trial specified in the protocol for that trial or (2) before the number of events required by the trial has occurred, the competent authority and ethics committee will be notified in writing of the termination of the trial within 15 days of the date of termination with a clear explanation of reasons and details of follow-up measures, if any, taken for safety reasons.

8.2 Clinical Trial Summary Report

The clinical trial summary report should be submitted to the competent authority within one year of submitting the end of trial notification. The content and format of the report should follow guidelines published on the MHRA website. The CI is responsible for compiling and submitting the final report to both sponsors and MHRA.

Clinical Trial results also require to be uploaded to the EudraCT database (https://eudract.ema.europa.eu/).

9 DATA HANDLING

CRFs will be supplied electronically to sites by CRUK Glasgow CTU Glasgow. These forms must be completed in accordance with the CRF Completion Guidelines issued with the CRFs.

Entries to the CRFs should be made in black ballpoint pen and must be legible. Any errors must be crossed out with a single stroke, the correction inserted and the change initialled and dated by the investigator or the appropriate site personnel with this delegated responsibility as noted on the Staff Contact and Responsibilities Sheet. Correction fluid must not be used.

Please ensure that all data submitted on CRFs are verifiable in the source documentation or that any discrepancies are recorded and explained.

9.1 Case Report Forms

Completed, original CRF pages should be sent to:

BALLAD UK Trial Clinical Trial Coordinator
Cancer Research UK Clinical Trials Unit
Level 0
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow

G12 0YN

Trial sites should keep a copy of all completed CRFs
All the CRFs must be returned for data entry and ultimately, statistical analysis.
CRFs from the trial will be stored in line with current regulatory requirements. Other essential documents, including source data, consent forms and regulatory documentation, will be archived by the investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

9.2 COVID-19 Pandemic

The COVID-19 pandemic has presented challenges for research across the UK. In order that the impact can be assessed correctly, extra data will be collected regarding patients recruited within the BALLAD study. This will be collected for patients at participating sites who have:

- Displayed symptoms of COVID-19
- Had a clinical diagnosis of COVID-19
- Had a test for COVID-19

The data which will be collected includes:

- Confirmation that patient has displayed symptoms of COVID-19
- Details of any COVID-19 tests the patient has had and results
- Whether or not the patient was hospitalised due to COVID-19
- Any impact COVID-19 had on the patient's participation in the trial

Any amendments made to the database by the CRUK Glasgow CTU during the course of the study will be detailed in a Data Rulings Document which will be circulated to all sites for information. Examples of these may include, but are not limited to:

- Marking fields/eforms as not applicable/not available
- Clearing DCFs which have been raised to site and are no longer applicable
- Clearing warnings when sites have responded satisfactorily to the query

All data will be managed as per the CRUK Glasgow CTU SOPs.

9.3 Data Return and Escalation Processes

CRUK Glasgow CTU will regularly chase outstanding data from participating sites. Routine requests for outstanding data and outstanding data queries will be performed quarterly or more regularly if required for a specific trial.

Sites will be routinely requested to return outstanding data and data queries within 6 weeks of receiving the queries or the CRF being due for completion.

Trigger reports will be run quarterly at the same point as the routine requests for data. If any site has 20% of forms overdue for more than 3 months (at least 10 forms meeting this criteria) or any forms greater than 6 months overdue the site will be contacted. A log will be kept of any sites meeting a trigger point. If a site consistently meets a trigger point an escalation process will be begin.

Data Escalation Process

Step 1: E-mail letter to site main contact and copy in site PI

Step 2: E-mail letter direct to site PI and copy in site main contact

Step 3 E-mail letter to CRN Research Delivery Manager (or equivalent) and copy in site PI and main contact

Step 4: Discuss suspension of recruitment at site until data issues resolved. These discussions will take place within the Trial Management Group (including the Chief Investigator and Sponsor)

For data queries CRUK Glasgow CTU will develop a data rulings document and resolve as many self evident queries as possible at site to minimise the queries sent to site.

9.4 Record Retention and archiving

To enable evaluations and/or audits from regulatory authorities the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), ensure subjects medical records are labelled appropriately and retained, all original signed informed consent forms, serious adverse events forms, source documents, and detailed records of treatment disposition in accordance with GCP, local regulations, or if a multi-centre trial, as specified in the CTA, whichever is longer. Archiving applies to both the participating site and the trial co-ordinating centre.

In the event that a patient's care is transferred to another hospital a Patient Transfer Form must be completed and returned to CRUK Glasgow CTU. The original randomising site will be recognised with the recruitment of the patient. The randomising site will continue to be responsible for returning all outstanding trial documents that are due until the date of transfer and any documents required after the date of transfer will be the responsibility of the site the patient was transferred to,

Participating sites are responsible for archiving their trial related documentation and should follow the requirements of their R&D Office in conjunction with advice from CRUK Glasgow CTU regarding the duration of document retention. CRUK Glasgow CTU will be responsible for archiving all other trial documentation that is not kept at participating sites.

10 TRIAL MANAGEMENT

10.1 Trial Start Up

Sites wishing to participate in the trial should contact the CRUK Glasgow CTU. A PI must lead the trial at each site and they will be responsible for providing CRUK Glasgow CTU with all core documentation. Protocol training will be given to sites via initiation slides that will be provided to sites prior to the trial opening at site. The site will be contacted by e-mail or fax when they are activated and are able to recruit patients to the trial

10.2 Core Documents

These documents consist of:

- Clinical Trial Agreement
- Site Contact Details
- Staff Contact and Responsibilities sheets for all members of the Trial team
- Confirmation of favourable Site Specific Assessment (SSA)/ Trust or Board R&D Approval letter/Confirmation of capacity and capability
- Local versions of Patient Information Sheets, Consent Forms and GP Letters on hospital headed paper
- Biochemistry and Haematology normal ranges and laboratory accreditation certificates
- Up to date, signed and dated CVs for all members of the trial team. The CV should detail the qualifications, experience and training (including GCP training) of site personnel relevant to their role in the trial, and should be updated every 2 years or as per local trust practise.

If circumstances change at the site (i.e. change of PI, hospital address etc.) new documents must be completed and sent with a cover letter to the CRUK Glasgow CTU.

10.3 Management of protocol deviations and violations

Incident Reporting

Organisations must notify the Sponsor (via CRUK Glasgow CTU) of all deviations from the protocol or GCP immediately. The Sponsor requires a report on the incident(s) and a form will be provided prior to site initiation. If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the CRUK Glasgow CTU trial team and Sponsor can be contacted immediately to discuss. The Sponsor will assess all incidents against the definition of a serious breach.

Serious Breach

In addition to the definition of a serious breach in GCP, systematic or persistent violation by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach. In cases where a potential or actual serious breach

has been identified, the Sponsor (via CRUK Glasgow CTU) will inform the MHRA within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the Sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches, 2009).

The Sponsor and CRUK Glasgow CTU will use an organisation's history of non-compliance to make decisions on further collaborations.

10.4 Trial Management Group (TMG)

A TMG will oversee the running of the trial. Members of the TMG will include the CI, Co-Investigators, Project Manager, Sponsor representative, Sponsor Pharmacist, Clinical Trial Co-ordinator, Trial Statistician, IT Staff, Quality Assurance Manager and Clinical Trial Monitor.

The TMG will meet every 2 months or as required, meetings may be by teleconference.

10.5 Trial Steering Committee (TSC)

A TSC will provide overall supervision for the trial. The TSC will be responsible for monitoring the progress of the trial towards its interim and overall objectives, focusing on adherence to the protocol, GCP, and patient safety. The TSC will include independent members who are not directly involved in other aspects of the trial. BALLAD UK and GLOBAL BALLAD will come under the CRUK Glasgow CTU's Umbrella Trial Steering Committee (UTSC).

In addition a GLOBAL BALLAD Trials Steering Committee (TSC) will be formed. This will consist of the BALLAD UK CI, BALLAD UK statistician, BALLAD UK project lead and two nominated representative from each of the participating trials in the GLOBAL BALLAD collaboration. This GLOBAL BALLAD TSC will be chaired the BALLAD UK CI and will meet approximately annually to review study progress.

Significant decisions made by the GLOBAL BALLAD TSC (e.g. re study design/reporting) are subject to review by the UTSC; the latter committee having primacy because of its independence.

The above TSC arrangements are also detailed in the GLOBAL BALLAD Charter.

10.6 Data Monitoring Committee (DMC)

A DMC will be established and will review the data from BALLAD UK and the GLOBAL BALLAD collaboration. The DMC will assess at intervals (planned or on request) the progress of the trial, the safety data, the critical efficacy endpoints, and will make any recommendations to the Sponsor and TMG whether to continue, modify or stop the trial.

11 REGULATORY ISSUES

The study will be conducted in line with the current Government, MHRA, HRA and health board guidance regarding COVID-19.

11.1 Clinical Trials Authorisation (CTA)

Clinical trial authorisation will be requested by CRUK Glasgow CTU on behalf of the Sponsor and they will maintain this throughout the trial. For the GLOBAL BALLAD trial each participating country will be responsible for ensuring all necessary approvals are in place before commencing recruitment into the trial.

11.2 Ethics Approval

Favourable ethical opinion will be sought before patients are entered onto this clinical trial. The CI will be responsible for updating the ethics committee of any new information related to the trial.
Each separate trial site will require Site Specific Approval (SSA) for each participating Trust or Board.
The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and as amended.

11.3 Consent

Consent to enter the trial or to tissue acquisition must be sought from each participant only after full explanation has been given, an information sheet offered and time allowed for consideration. Signed participant consent must be obtained, the consent forms should also be signed by the person carrying out the consent procedure at site, who must be detailed on the Staff Contact and Responsibility Log as having authorisation. The PI is responsible for ensuring if the taking of consent is delegated to a designee, the designee is suitably qualified by training or experience to take informed consent.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the best interests of the participant, but the reasons for doing so must be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the patient's medical records. All patients must be given an original or copy of the signed patient information sheet and consent form for their records. A Consent Notification Form must be submitted with the randomisation form. Consent forms must be retained on site and not submitted to the trials office.

In the event that new patient information sheets/consent forms are produced throughout the duration of the trial, it maybe that patients already participating in the trial should be re-consented to the updated version of the patient information sheet. However, if the PI decides that this is not in the best interests of the patient re-consent is not required. Decisions to not re-consent patients must be documented in the patient's medical records.

11.4 Confidentiality

All information collected during the course of the trial will be kept strictly confidential and only information that is directly relevant to the objectives and outcome measures detailed in the protocol will be collected. The collection of additional data not so specified is not permissible.

Information will be held securely on paper and electronically at the CRUK Glasgow CTU. The CRUK Glasgow CTU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

• Consent from participants to record personal details including initials, date of birth, sex at birth, CHI/NHS number, GP name and address.

• Appropriate storage, restricted access and disposal arrangements for patient's personal and clinical details

• Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation

• Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.

• Patient initials will be collected when a patient is randomised into the trial but all other data collection forms that are transferred to or from the CRUK Glasgow CTU will be coded with a trial number and will include two patient identifiers, usually the patient's initials and date of birth.

• Where central monitoring of source documents by CRUK Glasgow CTU (or copies of source documents) are required (such as scans or local blood results), the patient's name must be obliterated by site before sending.

• Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CRUK Glasgow CTU.

If a participant withdraws consent from further trial treatment and / or further collection of data their samples will remain on file and will be included in the final trial analysis unless they specifically withdraw consent for this.

• Note that trials involving tissue collection where potentially genomic analysis will be performed details on ethnicity will be collected to complement this analysis.

11.5 Liability, Indemnity and Insurance

The Hospital Trust/Health Board at each participating site is responsible for the following:

1. Acts and omissions of its own staff and others engaged by it, including the CTU and PI
2. Ensuring the appropriate insurance administered by the National Health Service Litigation Authority is in place
3. Ensuring any non-NHS employees involved in the clinical trial have Honorary Contracts with the Trust/Board to cover access to patients and liability arrangements.

These responsibilities are outlined and agreed within the Clinical Trial Agreement.

No special insurance is in place for patients in this trial other than standard NHS liability insurance providing indemnity against clinical negligence. This does not provide cover for non-negligence e.g. harm caused by an unexpected side effect of participating in a trial. The Sponsors have responsibility for ensuring that financial cover for damages or compensation arising from no fault harm is available to patients, where applicable. The co-sponsor, University of Glasgow, maintains clinical trials insurance. Cover for this clinical trial has been agreed under the current policy.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence or other negligent harm to patients under its duty of care. As this is a clinician led trial there are no arrangements for no-fault compensation

11.6 Sponsors

The University of Glasgow and NHS Greater Glasgow and Clyde will act as the co-sponsors for this trial. Delegated responsibilities will be assigned to the CRUK Glasgow CTU and NHS Trusts/Boards taking part in this trial. Details of responsibilities will be outlined in the clinical trial agreement that should be signed prior to site initiation.

11.7 Funding

This trial has been funded by CRUK for the UK sites. Any international sites that wish to take part in the GLOBAL BALLAD collaboration will need to apply for funding to run the trial in their country

11.8 Protocol Amendments

Any change to the trial protocol will require an amendment. Any proposed, non-administrative, protocol amendments will be initiated by the CI following discussion with the TMG and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsors. The CI will liaise with trial sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI, Lead Statistician and sponsor representative. Before the amended protocol can be implemented favourable approval must be sought from the original reviewing REC, trial Sponsor, MHRA and participating site R&D offices.

12 QUALITY ASSURANCE

12.1 Allocation of Trial responsibilities

The Sponsors of this clinical trial are the University of Glasgow and NHS Greater Glasgow and Clyde A Clinical Trial Agreement will be put in place between the Sponsors and each of the participating sites. This agreement outlines the responsibilities of each party's in the running of the trial as well as the CI, the CRUK Glasgow CTU and the PI at the Participating Site.

12.2 Co-Sponsor Responsibilities

The Sponsor's responsibilities will be for Authorisation and Ethics Committee opinion, GCP and Conduct, and Pharmacovigilance. The majority of the Sponsor's responsibilities have been delegated to the CI who performs these via the CRUK Glasgow CTU as the co-ordinating centre for the trial. As such, the main role of the Sponsor is to ensure that the CI and CRUK Glasgow CTU fulfil their responsibilities as outlined in the Clinical Trial Agreement and to ensure that any identified "risks" either have controls or action points put in place.

12.3 Chief Investigator (CI)

The CI has delegated the majority of his responsibilities to the CRUK Glasgow CTU. The CI is directly responsible for ensuring the protocol and any amendments are in place, for review of SAEs and determination if SAEs meet the criteria for a SUSAR. The CI is also responsible for providing advice and recommendations on medical issues that arise involving the management of the patients on the trial. From the perspective of the Sponsor and for regulatory/ethics purposes, the CI for the trial will be Prof Jeff Evans.

12.4 CRUK Glasgow Clinical Trials Unit (CTU)

The CRUK Glasgow CTU are responsible for the overall management of the clinical trial. This includes all regulatory submissions (ethics, R&D and CTA) and any amendments, all administration relating to the submissions and any amendments, circulation of all correspondence to participating sites, data management, monitoring of data quality and safety, ongoing communication with participating sites, management of SAE/SUSAR reporting, and where applicable the management of any financial arrangements.

12.5 Participating Site

The Participating Site is responsible for the management of the trial within their site. This includes ensuring local management approval has been given, ensuring the trial is conducted according to GCP requirements, and ensuring the appropriate insurance or indemnity is in place. The Participating Site is also responsible for arranging access for on-site monitoring and auditing as identified in the trial protocol and also for regulatory inspections.

12.6 Principal Investigator (PI)

The PI is responsible for the delegation of trial activities within their site and ensuring all personnel are adequately trained and qualified to carry out their responsibilities. The PI will be required to provide evidence of GCP training (usually a certificate) or undergo the required GCP training prior to the trial opening at their site. Regarding the management of patients within their site, the PI is responsible for the safety and wellbeing of trial patients, reporting any deviations from the protocol to the coordinating trial office as well as any SAEs or safety issues. Full details of the responsibilities of the PI are outlined in the Clinical Trial Agreement. Two original copies of this will be held – one with the Sponsor and the other at the participating site. A photocopy of the signed agreement will also be held at the coordinating trial office.

12.7 Audits and Inspections

Trial Investigators must permit trial related monitoring, audits, REC review and regulatory inspections as required, by providing direct access to source data, CRFs and other documents (patients' medical records, trial site file, and other pertinent data).

The trial may be subject to inspection and audit by University of Glasgow and NHS Greater Glasgow and Clyde and as Sponsors, the CRUK Glasgow CTU and other regulatory bodies, i.e. the MHRA, to ensure adherence to GCP. If an inspection is scheduled at any participating site, the site must notify the Sponsor at the earliest opportunity.

It is the sponsor's responsibility to inform the investigators of all intended audits and regulatory inspections involving the participating site. It is the investigator's responsibility to ensure appropriate resources at site and that the inspectors have access to all source data.

12.8 Central Monitoring

Trial sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. Trial staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have.

12.9 On Site and Telephone Monitoring

Participating trial sites will be monitored by the CRUK Glasgow CTU on behalf of the Sponsor by telephone or by site visit, or both, dependent on the risk associated with the trial and the site. The level of monitoring will be decided in advance by agreement between the Project Manager and Quality Assurance Manager with input from the sponsor. The PI will allow the trial staff access to source documents as requested. In addition, the pharmacy department responsible for the trial will be visited to allow monitoring of the pharmacy site file and review of security, storage and accountability of trial drugs (if applicable). Investigators and site staff will be notified in advance about forthcoming monitoring visits. On occasion, members of the CRUK Glasgow CTU monitoring team may be

accompanied by other staff from the unit for training purposes. Where a participating site is using electronic data reporting systems or electronic patient records and hard copies are not available, the CRUK Glasgow CTU monitor will require access to a computer for the duration of the visit in order to verify all relevant source data against the CRF. This may involve being given a temporary log-in. If this is not permitted by local policy, there must be a member of site staff available to provide access to the monitor.

13 PUBLICATION POLICY

The BALLAD UK study will not publish study results on its own, although it may publish methodological logistical aspects as approved by the GLOBAL BALLAD TSC.

The primary GLOBAL BALLAD manuscript(s) will address the two primary questions:-

1. Does adjuvant chemotherapy results in an improved outcome (DFS and OS) over observation alone after potentially curative surgery for stage I, II, III and IV SBA?

2. Does adjuvant fluoropyrimidine and oxaliplatin chemotherapy results in an improved outcome (DFS and OS) over fluropyrimidine alone after potentially curative surgery for stage I, II, III and IV small bowel adenocarcinoma?

Although it is presumed that there will be a single primary publication, differential recruitment rates or other considerations may make two separate publications, one for each question, more desirable; this is at the discretion of the GLOBAL BALLAD TSC.

The last author for GLOBAL BALLAD will be the BALLAD UK Chief Investigator. The remaining authors will consist of the members of the GLOBAL BALLAD TSC. The order of authorship will reflect the number of patients recruited by each countries specific BALLAD study. Additionally if any single site recruits more than 5% of the patients in total they can nominate a local investigator to appear on the authorship list; this will appear after the members of the GLOBAL BALLAD TSC. The recruitment calculation will be question specific if two separate publications are being prepared.

The Principal Investigators from all sites contributing to the GLOBAL BALLAD collaboration will be acknowledged in an appendix. Key operational staff from each country will also be acknowledged in the appendix (maximum 2 per country).

No individual study that is part of the GLOBAL BALLAD collaboration may publish its own results in isolation prior to the primary GLOBAL BALLAD publication.

Any subsequent manuscripts will have a primary author, a writing team, and continued inclusion of the GLOBAL BALLAD collaborative group as a group author, with full membership of the GLOBAL BALLAD TSC in an appendix. Order of authorship will be determine by the GLOBAL BALLAD TSC.

These publication arrangements are also set out in the GLOBAL BALLAD Charter,

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APPENDIX 1: ECOG PERFORMANCE STATUS

Grade	**ECOG Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX 2: EXPECTED TOXICITIES

The toxicities listed below are not exhaustive – please also refer to the current SmPC.

Toxicity of 5-FU

Common	Neutropenia Anaemia Thrombocytopenia Stomatitis and mouth ulcers Diarrhoea Anorexia Changes in taste Watery eyes or sensitivity to sunlight Venous tracking
Less common	Hand-foot syndrome Discoloration of the skin Rash or itching Skin sensitivity to sunlight Hair loss Discoloration of nails, loss of nails Cracking, peeling or excessively dry skin

Toxicity of Capecitabine

Common	Fatigue Diarrhoea Hand -foot syndrome Nausea and vomiting Skin reactions (increased pigmentation, itching, dry skin) Abnormalities in liver function tests. Anaemia Lymphopenia
Less common	Neutropenia Thrombocytopenia Abdominal pain Anorexia Stomatitis and mouth ulcers Numbness or tingling of hands and/or feet (usually associated with hand-foot syndrome) Swelling of the ankles and/or feet Fever Constipation Eye irritation Headache Joint and muscle pain

Common	Numbness or tingling of the hands or feet - *this condition may be exacerbated by exposure to the cold* Nausea and vomiting Diarrhoea Fatigue Anaemia Thrombocytopenia Constipation Changes in liver function tests, liver damage
Less common	Neutropenia Fever Headache Insomnia Stomatitis and mouth ulcers Anorexia Abdominal pain Back pain Abnormalities in renal function tests

APPENDIX 3: DETERMINATION OF CREATININE CLEARANCE (Cl_{CR})

Estimation of creatinine clearance using Cockroft and Gault method:

$$Cl_{CR} \text{ for males (mL/min)} = \frac{[140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$$

$$Cl_{CR} \text{ for females (mL/min)} = \frac{(0.85) \times [140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$$

For SI units:

$$Cl_{CR} \text{ for males (mL/min)} = \frac{[140 - \text{age (years)}] \times [\text{weight(kg)}] \times (1.23)}{[\text{Serum creatinine (µmol/L)}]}$$

$$Cl_{CR} \text{ for females (mL/min)} = \frac{[140 - \text{age(years)}] \times [\text{weight(kg)}] \times (1.04)}{[\text{Serum creatinine (µmol/L)}]}$$

Wright Equation

$$\text{Estimated GFR (ml/min)} = \frac{\{[6580 - (38.8 \times \text{age})] \times \text{BSA} \times [1 - (0.168 \times \text{sex})]\}}{\text{Serum Creatinine (µmol/L)}]}$$

Sex: male = 0; female = 1; BSA, body surface area (DuBois)

Calculation of creatinine clearance based on 24-hour urinary creatinine excretion and concurrent serum creatinine levels:

$$Cl_{CR} = \frac{C_U \cdot V}{C_{CR}}$$

Here, C_U is the concentration of creatinine in the urine (mg/dL or µmol/L, for SI units), V is the urine volume (in mL per minute of urine produced during the collection period), C_{CR} is the serum creatinine concentration (mg/dL or µmol/L, for SI units), and Cl_{CR} is the creatinine clearance in mL per minute.

APPENDIX 4: NEW YORK HEART ASSOCIATION STAGING (NYHA)

- **Class 1:** Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
- **Class 2:** Subjects with slight, mild limitation of activity; they are comfortable with rest or mild exertion.
- **Class 3:** Subjects with marked limitation of activity; they are comfortable only at rest.
- **Class 4:** Subjects who should be at complete rest, confined to a bed or chair, any physical activity brings on discomfort and symptoms occur at rest.

APPENDIX 5: EORTC QLQ-C30 & CR29 (COLORECTAL MODULE)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birth date (Day, Month, Year): _____/_____/_____

Today's date (Day, Month, Year): _____/_____/_____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the Day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4

	During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhoea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Please go on to the next page

CR29 (colorectal module)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

Please go on to the next page

Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:

49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4
For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

APPENDIX 6: EQ-5D QUESTIONNAIRE

Please note that questionnaire **must** be completed by the **patient**.

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities(*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

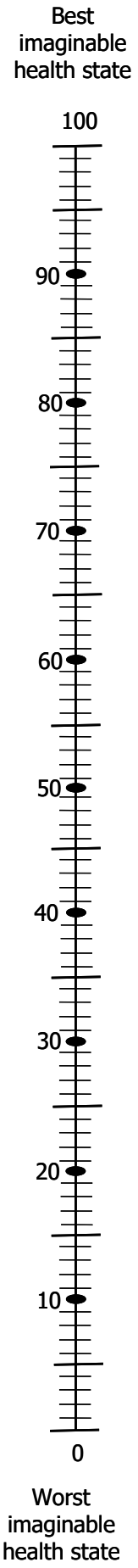
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 7: SMALL BOWEL RISK FACTOR QUESTIONNAIRE

DATE QUESTIONNAIRE COMPLETED: DD / MON / YYYY

Please circle the appropriate answer

Have you been diagnosed with any of the following?:			
Crohn's disease	Yes	No	Unknown
Coelic disease	Yes	No	Unknown
Lynch Syndrome	Yes	No	Unknown
Inflammatory bowel disease	Yes	No	Unknown
Familial Adenomatous Polyposis (FAP)	Yes	No	Unknown
Peutz-Jeghers Syndrome	Yes	No	Unknown
Hereditary non-polyposis colorectal cancer	Yes	No	Unknown
Cystic Fibrosis	Yes	No	Unknown
Peptic Ulceration	Yes	No	Unknown

Are you a smoker?	Yes	Never	Former smoker	
If yes	Please give number of years you have been smoking			_____
If former smoker	Please estimate how many years you smoked			_____

Does any member of your immediate family (mother, father, brothers and sisters) have a history of gastric cancer?	Yes	No

APPENDIX 8: DECLARATION OF HELSINKI 2008

Please go to the following website to access the Declaration of Helsinki (2008).

http://www.wma.net/en/30publications/10policies/b3/

APPENDIX 9: BALLAD TUMOUR STAGING GUIDELINE

TNM staging		Eligible for BALLAD?
Tis, N0, M0	Stage O	No
T1, N0, M0 T2, N0, M0	**Stage I**	**Yes**
T3, N0, M0	**Stage II A**	**Yes**
T4, N0, M0	**Stage II B**	**Yes**
T1, N1, M0 T2, N1, M0	**Stage III A**	**Yes**
T3, N1, M0	**Stage III B**	**Yes**
T4, N1, M0	**Stage III B**	**Yes**
T1, N2, M0 T2, N2, M0 T3, N2, M0	**Stage III C**	**Yes**
T4, N2, M0	**Stage III C**	**Yes**
Any T, Any N, M1	**Stage IV**	**No ***

*** YES IF SEEN AFTER A R0 RESECTION OF ALL KNOWN METASTATIC DISEASE**

APPENDIX 10: EFFECTIVE METHODS OF CONTRACEPTION

Female patients who are not surgically sterile or post-menopausal must agree to use effective contraception during the period of therapy and for 6 months after discontinuation of trial treatment. NB: Post-menopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential.

Male patients must be surgically sterile or agree to use effective contraception during the period of therapy and for 6 months after discontinuation of trial treatment.

Effective methods of contraception include:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomised partner who is sterile prior to the female patient's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, during the period of therapy and for 6 months after discontinuation of trial treatment.

Note: Oral contraceptives are not reliable due to potential drug-drug interactions.