In collaboration with:

Study Title:	Neo-AEGIS (NEO-adjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction.
Study Number:	CTRIAL-IE [ICORG] 10-14
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EUDRACT Number:	2011-001858-28
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PROTOCOL AUTHORISATION

Study Title:	Neo-AEGIS (NEO-adjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction
Study Number:	CTRIAL-IE [ICORG] 10-14
Version/date:	Version 12 / dated 27-Jul-2020

The protocol is approved by the following:

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Name	Signature	Date (dd-MON-yyyy)

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LIST OF ABBREVIATIONS

Abbreviation/Acronym	Full Form
AE	Adverse Event
AEG	Adenocarcinomas of the esophagogastric junction
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
ASA	American Society of Anesthesiologists – Grading system
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Atrioventricular
BSA	Body surface area
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CAP	College of American Pathologists
CMO	Cystoid Macular Oedema
CF	Cisplatin, 5-fluorouracil
COPD	Chronic Obstructive Pulmonary Disease
CPEX	Cardio-Pulmonary exercise testing
CRF	Case report form
CrCl	Creatinine Clearance
CRT	Conformal Radiation Therapy
CSA	Country Specific Appendix
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT-PET	Computed Tomography Positron Emission Tomography
DNA	Deoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
Dr	Doctor
DSMB	Data Safety Monitoring Board
ECF	Epirubicin, Cisplatin, 5-Fluorouracil
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group (ECOG)
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ECX	Epirubicin, cisplatin, capecitabine
EDTA	Ethylenediaminetetraacetic acid

EOF	Epirubicin, oxaliplatin, fluorouracil
EORTC-QLQ C30 (Including EORTC QLQ-OES 18)	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Oesophageal 18 Questionnaire
EOX	Epirubicin, oxaliplatin, capecitabine
EUS	Endoscopic Ultrasound
FBC	Full blood count
FEV	Forced expiratory Volume
FDG-PET	(^{18}F) Fluorodeoxyglucose positron emission tomography
FLOT	5-fluorouracil (F), Leucovorin (L), Oxaliplatin (O), Docetaxel (T)
5FU	5-fluorouracil
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSA	Group Specific Appendix
HCG	Human Chorionic Gonadotropin
HRQL	Health Related Quality of Life
HIV	Human Immunodeficiency Virus
ICH GCP	International Conference on Harmonization Good Clinical Practice
ICRU	International Commission on Radiation Units and Measurements
CTRIAL-IE	Cancer Trials Ireland
IMP	Investigational Medicinal Product
INR	International normalised ratio
ITT	Intention to treat
IMRT	Intensity Modulated Radiation Therapy
IV	Intravenous
LB	Lower Bound
LDH	Lactate dehydrogenase
LVEF	Left Ventricular Ejection Fraction
LV	Leucovorin
MAGIC	Medical Research Council Adjuvant Gastric Infusional Chemotherapy
MDT	Multi-Disciplinary Team
MRC	Medical Research Council
MUGA	Multiple gated acquisition scan
NaCl	Sodium Chloride
NCI	The National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OAR	Organs at risk

OGD	Oesophago-gastro-duodenoscopy
OGJ	Oesophago-gastric Junction
OS	Overall survival
PAF	Plan Assessment Form
pCR	Pathologic complete response
PCR	Polymerase Chain Reaction
PCV	Polyvinyl Chloride
PFT	Pulmonary Function Test
PO	By mouth / orally
PT	Prothrombin time
QA	Quality Assurance
RCP	Royal College of Pathology
RCT	Randomised Controlled Trial
RNA	Ribonucleic acid
RT	Radiotherapy
RTTQA	Radiotherapy Trials Quality Assurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCC	Squamous cell carcinoma
SDMO	Statistics and Data Management Office
SIM	Specialised Intestinal Metaplasia
SmPC	Summary of product characteristics
SWOG	South West Oncology Group
TNM	Tumour Nodes Metastases
TSC	Trial Steering Committee
TRG	Tumour Regression Grade
UB	Upper Bound
ULN	Upper Limit Normal
UICC	TNM Committee of the International Union against Cancer
WBC	White blood count
3DCRT	3-Dimensional Conformal Radiation Therapy
4DCT	4-Dimenstional Computed Tomography

1. Study Synopsis

Sponsor	Cancer Trials Ireland
Study No./ Short study title:	CTRIAL-IE [ICORG] 10-14 / Neo-AEGIS
Study Title	**Title of Trial: Neo-AEGIS (NEO-adjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction**
EUDRACT No:	2011-001858-28
Investigational Medicinal Product(s) **Test and Comparator:**	**Indication:** Patients with cT2-3 N0-3 M0 adenocarcinoma of the oesophagus or junction, based on clinical, CT-PET, and EUS staging, will be randomised to neoadjuvant and adjuvant chemotherapy and surgery versus the CROSS neoadjuvant chemoradiation protocol prior to surgery. Patients will be randomised to either Arm A neoadjuvant and adjuvant chemotherapy (Investigator choice modified MAGIC (ECF/ECX or EOF/EOX) or FLOT regimen) and surgery or Arm B (CROSS protocol: chemotherapy with radiation therapy and surgery as per multimodal protocol). The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use (modified MAGIC (ECF/ECX or EOF/EOX) or FLOT) are to be made by the treating clinician. **NOTE:** Dose rounding is permitted. Chemotherapy agents can be rounded up or down as per institutional practise (e.g.: epirubicin to nearest 2mg, oxaliplatin to nearest 5mg, 5-fluorouracil to nearest 5mg, capecitabine as 150mg and 500mg tablets.). Dose banding is permitted in the trial to a maximum of 6% variance from the calculated dose. **Arm A: Modified MAGIC** The modified MAGIC regimen encompasses 3 cycles of chemotherapy pre-surgery and 3 cycles post-surgery. The regimen is a combination of epirubicin, cisplatin or oxaliplatin and a choice of 5-fluorouracil or capecitabine. The choice between administering cisplatin or oxaliplatin and 5-fluorouracil or capecitabine is at the discretion of the investigator. Each cycle lasts 21 days and consists of the following:

Drug	Dose	Administration	Days Given
Epirubicin	50 mg/m^2	Slow IV push into the side arm of Sodium Chloride (NaCl) 0.9% drip	Day 1
Cisplatin with hydration - mannitol 10%* OR Oxaliplatin	60 mg/m^2 500 ml 130 mg/m^2	Dilute in NaCl 0.9%. Administer over 2 hours. Infuse concurrently with cisplatin over 2 hours Dilute in Dextrose 5%. Administer over 2 hours	Day 1
5-fluorouracil OR Capecitabine	200 mg/m^2/day 625 mg/m^2 twice daily	Given at a dose of 200 mg/m^2/day by continuous infusion every day for 21 days/3 weeks Taken orally twice daily for 21 days	Days 1-21 Days 1-21

All chemotherapy agents must be stored, prepared, and administered according to the manufacturer's SmPC.

Frequency of epirubicin and cisplatin/oxaliplatin: Day 1 of every 21 day cycle
Frequency of 5-fluorouracil/capecitabine: Every day continuously for 3 cycles pre-operatively and 3 cycles post-operatively
**** Note: The use of mannitol and pre/post hydration will be carried out as per the institution's and local standard practice at the discretion of the treating physician, if different from the above guidelines.***

Arm A: FLOT
The FLOT regimen encompasses 8 cycles of chemotherapy in total, 4 cycles of chemotherapy pre-surgery and a further 4 cycles of chemotherapy post-surgery. Each cycle of chemotherapy lasts 14 days/2 weeks and consists of the following:

Drug	**Dose**	**Administration details**	**Days given**
Docetaxel	50 mg/m²	Administer over 1 hour IV Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
Oxaliplatin*	85 mg/m²	Administer over 2 hours IV Dilute in glucose 5%	Day 1 of each cycle
Leucovorin*	200 mg/m²	Administer over 2 hours IV Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
5-fluorouracil	2600 mg/m²	Administer over IV 24 hours infusion Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
Dexamethasone or	8 mg	PO twice daily	Day before, day of and day after

equivalent	Or dose and administration per standard practice
Frequency of FLOT: Every 14 days	

All chemotherapy agents must be stored, prepared, and administered according to the manufacturer's SmPC.

Arm B: CROSS

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive. The chemotherapy regimen consists of the following:

Drug	Dose	Administration Details	Days Given
Dexamethasone or equivalent	Dose and administration per local standard practice.		Days 1, 8, 15, 22 and 29
Chlorphenamine (Piriton) or equivalent	Dose and administration per local standard practice.		Days 1, 8, 15, 22 and 29
Ranitidine (Zantac) or equivalent/alternative	Dose and administration per local standard practice.		Days 1, 8, 15, 22 and 29
Paclitaxel	50 mg/ m^2	The total calculated dose of paclitaxel, will be infused over 1 hour IV (polyvinyl chloride (PVC) Free).	Days 1, 8, 15, 22 and 29
Ondansetron or equivalent	Dose and administration per local standard practice.		Days 1, 8, 15, 22 and 29
Carboplatin Area Under Curve =2	As per calculation	The total calculated dose of carboplatin, will be infused over 1 hour IV.	Days 1, 8, 15, 22 and 29

All chemotherapy agents must be stored, prepared, and administered according to the manufacturer's SmPC.

The absolute dose of carboplatin will be calculated for the target Area Under Curve (AUC) =2 according to the Calvert formula:
The absolute dose of Carboplatin =
(Target AUC) X (Glomerular Filtration Rate + 25)

Cockcroft/Gault formula to be used for GFR calculations:

$$= \frac{N\,(140-age) \times weight\ (kg)}{Serum\ creatinine\ (micromol/L)}$$

Where N = 1.04 for females, and 1.23 for males

Study Objectives:	**Primary Objective:** To evaluate one, two and three year survival of patients treated with resection plus neoadjuvant and adjuvant chemotherapy versus resection plus neoadjuvant chemo radiotherapy.

	Secondary Objective(s): To evaluate the effect of both neoadjuvant regimens on clinical and endoscopic response rate (in particular relief of dysphagia, improvement in health related quality of life (HRQL) and endoscopic regression), tumour regression grade, surgical resection rate (including resectability and pathologic R0 resection), post-operative pathology, disease-free survival, time to treatment failure, site of treatment failure, toxicity and post-operative complications. **Exploratory Objective(s):** Translational Research: The collection of blood and tissue samples for storage in the biobank for future research
Study Design:	This is a multicentre phase III open-labelled, randomised controlled trial. Eligible patients will be randomised in a 1:1 fashion between neoadjuvant and adjuvant chemotherapy (Investigator's choice modified MAGIC (ECF/ECX or EOF/EOX) or FLOT regimen) and surgery or Arm B (CROSS protocol: chemotherapy with radiation therapy and surgery as per multimodal protocol).
Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Histologically verified adenocarcinoma of the oesophagus or oesophago-gastric junction based on endoscopy (OGD). 2. CT-^{18}FDG-PET performed in all patients for disease staging. 3. EUS in all patients unless luminal obstruction precludes sensitivity of the test. 4. Staging laparoscopy performed at the investigator's discretion for locally advanced AEG II and AEG III tumours. 5. Pre-treatment stage cT2-3, N0-3, M0. 6. Maximum tumour length should be no more than 8 cm (equal to 8 cm is acceptable). 7. Male/female patients aged ≥18 years. 8. ECOG Performance Status 0, 1 or 2 (Appendix D). 9. ASA I-II (Appendix D). 10. Adequate cardiac function. For all patients, an ejection fraction of > 50% is required. If patients have a known cardiac history (e.g. known ischemic disease, cardiomyopathy) an ejection fraction > 50% and cardiac clearance by a consultant cardiologist for major surgery and cancer therapies is required. 11. Adequate respiratory function. Patients should have pulmonary function tests completed with a minimum FEV1 ≥ 1.5L. CPEX acceptable. 12. Adequate bone marrow function: absolute neutrophil count (ANC) >1.5x10^9/l; white blood cell count >3x10^9/l; platelets >100x10^9/l; haemoglobin (Hb) >9g/dl (can be post-transfusion). 13. Adequate renal function: glomerular filtration rate >60ml/minute calculated using the Cockcroft-Gault Formula (Appendix M). 14. Adequate liver function: serum bilirubin ≤ ULN; AST <2.5x ULN and ALP <3x ULN (ULN as per institutional standard). 15. Written informed consent must be obtained from the patient before any study-trial specific procedures are performed. 16. Women of child-bearing potential and male subjects must agree to use an effective barrier method of contraception for up to 6 months following discontinuation of therapy. Effective contraception is defined as any medically recommended (or combination of methods) as per standard of care. 17. Women of childbearing potential must have pregnancy excluded by urine or serum beta-HCG testing within 7 calendar days prior to registration.

	Exclusion Criteria 1. Tumours of squamous histology. 2. Patients with advanced inoperable or metastatic oesophageal, junctional or gastric adenocarcinoma. 3. Disease length (total length of tumour plus node) greater than 10 cm (up to 10 cm will be allowed) *-as measured by any modality or, if appropriate, combination of modalities-,* unless in the opinion of the investigator in discussion with national RT lead, it is felt that Organ At Risk (OAR) constraints are likely to be achievable. 4. Any prior chemotherapy for gastrointestinal cancer. 5. Prior abdominal, thoracic, chest wall or breast radiotherapy. 6. Patients who are unfit for surgery or cancer treatments based on cardiac disease. 7. Patients with acute systemic infections. 8. Patients who are receiving treatment with sorivudine or its chemical related analogues, such as brivudine which is contraindicated with capecitabine and 5-fluorouracil administration. 9. Clinical Chronic Obstructive Pulmonary Disease (COPD) with significant obstructive airways disease classified by FEV1 < 1.5 L or PaO_2 less than 9kPa on room air 10. Known peripheral neuropathy >Grade 1 (absence of deep tendon reflexes as the sole neurological abnormality does not render the patient ineligible). 11. Known positive tests for human immunodeficiency virus (HIV) infection, acute or chronic active hepatitis B infection. 12. Any other malignancies within the last 5 years (other than curatively treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix) 13. Participation in other clinical trials of investigational or marketed agents for the treatment of oesophageal cancer or other diseases within 30 days from registration. UK sites please refer to Group Specific Appendix 14. Women who are pregnant or breastfeeding. 15. Psychiatric illness/social situations that would limit compliance with study requirements 16. Known Dihydropyrimidine dehydrogenase (DPD) deficiency For sites in UK, France, Denmark, Sweden and Netherlands: for inclusion and exclusion criteria please refer to your (applicable) Group Specific Appendices (GSA) / Country Specific Appendices (CSA).
Primary and Secondary Efficacy Endpoints:	Primary endpoint: • Overall survival Secondary endpoints: • Clinical and endoscopic response rate • Tumour Regression Grade • Surgical Resection Rate ((i) Resectability & (ii) Pathologic R0 resection) • Post-operative pathological staging • Disease-free survival • Time to treatment failure • Site of treatment failure • Toxicity • Post-operative complications

	• EORTC C30 Health Related Quality of life
Exploratory Objectives	Translational Research: The collection of blood and tissue samples for storage in the biobank for future research (specific to Irish sites only)

2. Background and Rationale

2.1 Introduction

Adenocarcinoma of the oesophagus and oesophagastric junction (OGJ) have increased in incidence in the West over the last quarter century[1]. Adenocarcinoma at the oesophago-gastric junction (AEG) has been defined topographically by Siewert et al., with true oesophageal (AEG1) tumours arising in a background of reflux-induced specialised intestinal metaplasia (SIM)[2]. The majority of true cardiac (AEG2) and all sub-cardiac junctional tumours (AEG3) arise from gastric epithelium and in contrast to AEG1, have no simple disease paradigm, but reflect the trend for a proximal shift in the site of gastric tumours to the proximal stomach or junction. Oesophageal and junctional adenocarcinoma may be advanced at presentation, and the overall 5-year survival remains dismal at between 10-20 per cent[1]. For patients presenting with localized disease, several advances in standards of care have emerged in recent years which have improved disease management. Firstly, comprehensive staging with Computed Tomography (CT), endoscopic ultrasound (EUS) and fluoro deoxy glucose positron emission tomography (^{18}FDG-PET) permits exclusion of patients for curative therapy who might previously have undergone resection[1]. Secondly, unassailable evidence supports the case for oesophagectomy to be performed in high-volume hospitals by high-volume surgeons, and this has been supported in many countries by action from funders, government, and the profession itself[3]. Finally, neoadjuvant and adjuvant therapies are considered in most centres for patients with localized oesophageal adenocarcinoma, and, although controversial, subgroups of patients may benefit from this approach.

The surgical principle of oesophageal, junctional and gastric adenocarcinoma is to perform a wide clearance, achieve a negative margin (R0 resection), and perform a radical lymphadenectomy. The approach to achieve this is not standardised, and the lack of surgical quality assurance has been a problem in many of the randomised trials of neoadjuvant and adjuvant therapy (*vide infra*). The best results for oesophageal cancer in surgery-only series have been achieved in selected series by en-bloc resection and lymphadenectomy which may achieve a cure rate of approximately 50 per cent, and similarly for gastric cancer by wide clearance combined with D2 lymphadenectomy[4-7]. Beyond good quality cancer surgery, outcomes can be improved by neoadjuvant or adjuvant chemotherapy with or without radiation therapy. In the following section the relevant key randomised trials will be reviewed, as the premise for the study proposed is based on the gaps in Level I evidence pertaining to subgroups of patients with cancer at these sites.

2.2. Review and Appraisal of Randomised Trial

2.2.1. Current Practice

The UK standard practice for oesophageal and junctional adenocarcinoma is increasingly neoadjuvant chemotherapy prior to resection, based largely on the MAGIC and OEO 2 data. Pre- and post-operative chemotherapy is also commonly practiced in many major European Centres. In Ireland and in some centres in Europe, but largely in North America, neoadjuvant chemoradiation is increasingly the standard of care for locally advanced tumours. Up to recently this was based largely on a randomised controlled trial (RCT) carried out at St. James's Hospital, Dublin, Ireland between 1990 and 1995, which compared surgery with multimodality therapy,

and meta-analyses. The most significant recent development in the use of neoadjuvant chemoradiation comes from a Dutch trial (CROSS trial) [8,9]. This proposed study is to directly compare these regimens (investigator's choice of modified MAGIC or FLOT regimen vs CROSS protocol) in a RCT. The trial is also unique in that all patients will be comprehensively staged pre-randomisation and surgical, medical, radiological, and pathological quality assurance will be established *a priori*. Patients will be randomised to either Arm A (investigator's choice of modified MAGIC or FLOT regimen of chemotherapy pre and post-surgery) or Arm B (multimodal arm: chemotherapy with radiation therapy pre surgery as per CROSS protocol).

2.2.2. Chemotherapy

There are five key studies (Table 1). An appropriately powered Phase III randomised study of 467 North American patients (US Intergroup 0113) showed no benefit from pre- and post-operative combination 5-fluorouracil and cisplatin, with a 2-year survival of 35% in the combination group compared with 37% in the surgery alone group, and a median survival of 15 and 16 months respectively [10]. A complete pathological response was observed in 2.5% of cases. In contrast, a similarly powered study of 802 patients conducted by the Medical Research Council, the OEO2 Trial, which randomised patients (adenocarcinoma and squamous cell cancer) to 2 cycles of pre-operative cisplatin and FU vs. surgery alone, reported a significantly improved survival at two years (43% vs. 34%) in the combined modality group, and an improved median survival of 16.8 vs. 13.3 months [11]. The principal differences between the Intergroup and MRC study was that the total pre-operative chemotherapy administered was greater in the Intergroup trial, there was a longer delay to surgery (median 93 vs. 63 days), and the median survival in the surgery alone arm was improved (16 vs. 13 months). Notwithstanding the different outcomes in both studies, in the UK, neoadjuvant chemotherapy is accepted as the standard of care.

The findings of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial provides further support for proponents of neoadjuvant chemotherapy for both oesophageal and gastric tumours[12]. This phase III trial randomly assigned patients with resectable adenocarcinoma of the stomach, oesophagogastric junction, or lower oesophagus to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). Chemotherapy consisted of three pre-operative and three post-operative cycles of intravenous epirubicin and cisplatin and a continuous intravenous infusion of fluorouracil (ECF). Post-operative morbidity and 30-day mortality did not differ between the two arms (46% versus 45% and 5.6% versus 5.9%, respectively). Compared with patients receiving surgery alone, the patients on the trial regimen had significantly improved overall (P=0.009) and progression-free survivals (P<0.001). The 5-year survival rate was 36% for combined modality therapy compared with 23% for patients with surgery alone. In the MAGIC trial, approximately 75% of patients had gastric tumours, 14% had tumours of the lower oesophagus and 11% had junctional tumours. The effect was consistent for each site, with a hazards ratio of 0.81, 0.44 and 0.75 for gastric, junction and oesophageal respectively. The principle of neoadjuvant therapy is supported by MAGIC, but the trial was not powered to address junctional and oesophageal adenocarcinoma and therefore no Grade A recommendation is provided for tumours at these sites.

A new dimension in the use of chemotherapy in upper gastrointestinal cancer was provided through the United Kingdom National Cancer Research Institute REAL2 trial. This multicentre trial with a 2x2 randomisation showed the non-inferiority of substituting capecitabine for infused 5FU, and oxaliplatin for cisplatin, in the ECF regimen[13-15]. These results support the use of capecitabine instead of infused 5FU in this regimen, a practice which is already in widespread clinical use. The oral administration of capecitabine improves the convenience and acceptability of the regimen by eliminating the need for central venous catheters and their associated complication risks, as well as being less of an imposition for patients. In addition, REAL2 established the non-inferiority of oxaliplatin with cisplatin, with oxaliplatin associated with lower incidences of grade 3 or 4 neutropenia, renal toxicity and thromboembolis, albeit with slightly higher incidences of grade 3 or 4 diarrhoea and neuropathy[13-15].

The recent FLOT4 (NCT01216644) trial showed perioperative chemotherapy with docetaxel, oxaliplatin, and 5-fluorouracil and leucovorin (FLOT) significantly improved progression-free survival (PFS) and overall survival (OS) among patients with resectable gastric or OGJ adenocarcinoma compared with epirubicin, cisplatin, and 5-fluorouracil or capecitabine (ECF/ECX).[38] Of 716 patients enrolled, 360 patients received ECF/ECX and 356 patients received FLOT. After a median follow up of 43 months, median OS was 35 months with ECF/ECX and 50 months with FLOT (hazard ratio, 0.77; P = .012).[38] Three-year OS was 48% for ECF/ECX and 57% for FLOT. FLOT also significantly improved PFS, with a median of 30 months with FLOT and 18 months with ECF/ECX. Perioperative complications were similar across the 2 arms: 50% with ECF/ECX and 51% with FLOT. More cases of grade 3 to 4 nausea and vomiting were seen with ECF/ECX and more cases of grade 3 to 4 neutropenia were seen with FLOT. Even though the FLOT4 study is not yet published, many centres across Europe are beginning to offer this chemotherapy regimen as alternative to the MAGIC regimen (ECX), with both regimens to be considered as standard of care at present. Therefore, the Neo-AEGIS protocol allows for the use of the FLOT regimen. By allowing the use of different accepted standards, the trial remains relevant, and the results applicable to 'real world' clinical practice.

2.2.3: Chemo radiotherapy

The interpretation of trials of combination chemotherapy and radiation therapy (Table 2) prior to surgery, and meta-analysis, is more difficult compared with trials using chemotherapy alone, for several reasons:
- Only 2 of 9 studies, both negative, appear adequately powered;
- There is a mix of pathologic types, adenocarcinoma and squamous cell cancer in all but one study;
- The total dose of radiation therapy administered, and treatment fractions, is different across trials;
- Pre-treatment staging used for these trials was either absent or outmoded compared with modern standards; and
- Interpretation of the only positive published trial showing a benefit for multimodal therapy may be compromised by relatively small numbers, no cross-sectional imaging in pre-treatment staging, and an outcome in the surgery alone arm (6% 3-year survival) below standard benchmarks[1, 16].

A large adequately powered Australasian study of 256 patients, 61% of whom had adenocarcinoma, failed to show a survival benefit to neoadjuvant chemo radiotherapy (CF x 4 cycles; 35Gy/15 fractions) [17].

Notwithstanding the relatively tenuous data from which it is drawn, these trials have resulted in widespread adoption of combination chemotherapy and radiation therapy, particularly in the United States. Apart from the St. James's Hospital trial, and meta-analysis[18] influenced by this data, proponents of this approach also cite proxy evidence from the other trials and Phase II studies. In the negative Australasian study, for instance, cancer outcomes including the R0 resection rate (80% vs. 59%) and node negativity (67% vs. 43%) were significantly greater in the multimodal group[17]. In the University of Michigan trial of 100 patients, powered for median survival, overall survival was 30% improved in the treated (CF and vinblastine; 45Gy/1.5 Gy fractions) arm vs. surgery alone cohort (p=0.15)[19]. A Phase III Trial (CALBG 9781) that recruited 56 patients of a planned 475 before closing due to poor accrual, showed a median survival of 4.48 years vs. 1.79 years favouring the treated (CF; 56Gy / 1.8Gy per fraction)[20]. The approach is indirectly supported by evidence including our own published experience that patients achieving a complete or major pathological response, seen in approximately 20-30% of traditional regimens, have an approximate 50% chance of cure[21, 23]. In this latter regard, new approaches to increase the complete pathological response rate would appear to have a sound rationale. The addition of paclitaxel to cisplatin and 5-fluorouracil based regimens have increased pathological Complete Response (pCR) rates but may result in significant toxicity[23, 24]. A recent study using a paclitaxel, carboplatin and 5-fluorouracil chemo radiotherapy regimen in patients with stage II and III disease but with a reduced paclitaxel dose demonstrated that acceptable toxicity along with a complete pathological response rate of 38% and R0 resection rate of 96% [25].

The most significant recent development in the use of neoadjuvant chemoradiation comes from a Dutch trial (CROSS trial) [8,9]. In this study, patients (n = 363) with resectable (T2-3, N0-1) oesophageal tumours were randomised to multimodal therapy (paclitaxel, carboplatin and 41.4 Gy/23 fractions RT) or surgery alone. The median survival was 49 months in the multimodal arm compared with 26 months for surgery alone in patients with oesophageal or junctional tumours. One, 2 and 3-year survival rates were 82%, 67% and 59% in the CRT arm and 70%, 52% and 48% in the surgery alone arm. Leukopenia occurred in 7% of patients, and non-haematological toxicities were all less than 5 per cent.

For gastric and junctional cancers, adjuvant post-operative chemoradiation has been evaluated in a trial of 556 patients performed by the Southwest Oncology Group (SWOG) and reported by Mac Donald et al in 2001 [26]. All patients had stage IB to IV M0 disease and underwent curative resections with negative margins. The adjuvant treatment consisted of 425 mg of FU and 20 mg leucovorin/m^2/d, for five weeks, followed by 4500 cGy or radiation at 180 cGy per day, given 5 days per week for 5 weeks, with modified doses of FU and LV on the first four and last three days of radiotherapy. One month after the completion of radiotherapy, two five-day cycles of FU (425 mg/m^2/d) plus leucovorin (20 mg/m^2/d) were given one month apart. The median overall survival in the surgery-only group was 27 months, as compared with 36 months in the chemo radiotherapy; the hazard ratio for death was 1.35.

In our view the excellent results reported for the CROSS trial define this currently as the multimodal standard of care, the MAGIC or FLOT regimens are the optimal chemotherapy regimen, and accordingly the proposed trial will compare these evidence-based approaches.

For many years, 3 Dimensional Conformal Radiation Therapy (3D CRT) has been the standard of care radiotherapy technique. However, increasingly Intensity Modulated Radiation Therapy (IMRT) is being utilised to reduce the radiation dose to surrounding organs while maintaining tumour control.[40,41] However, caution must be applied as even low doses of radiation, such as those received by the lungs using IMRT may result in a higher rate of pulmonary complications, including radiation pneumonitis.[42,43,44] With this mind, conservative guidelines have been prepared for sites using IMRT in this study.

2.3. Rationale for Proposed Studies

2.3.1. Weaknesses of Existing Trials

1. The MAGIC trial, although positive, was powered only for gastric cancer and not for junctional tumours, and there was no surgical quality assurance factored into the study.
2. Prior to the CROSS trial, all trials of pre-operative chemoradiation for oesophageal cancer are weakened by relatively small numbers, a mixture of pathological types, no standardisation of surgery and radiation therapy, and absent or inadequate staging prior to randomisation. CROSS includes squamous cell as well as adenocarcinoma, and compares multimodal with surgery alone.
3. Pre-randomisation staging varied from no cross-sectional imaging to CT scanning, and few trials have encompassed EUS, and none have used CT-PET.
4. The FLOT4 trial included a different patient population and had a different surgical management plan. In comparison to the population of the Neo-Aegis trial the FLOT4 trial included patients with resectable gastric as well as OGJ adenocarcinoma. Only 56% of the patients included in FLOT4 had OGJ adenocarcinoma. In addition, only 28% underwent Thoracic surgery.

2.3.2. Strength and Unique Elements of Proposed Studies

This will be the first trial powered specifically on this cohort, and where all eligible patients will have comprehensive pre-treatment staging that includes a determination of actual or predicted nodal status based on CT-PET, EUS $\pm$ laparoscopy. Modern quality assurance in surgery and pathology will also be

applied, with the goal of achieving an R0 radical resection in all cases, and a radical lymphadenectomy as standard. The 7th edition AJCC/UICC TNM (Appendix F) classification enables uniform pathological staging, in particular nodal, across the entire spectrum of adenocarcinoma of the oesophagus and junction, whereby there was a mix of oesophageal and gastric staging systems [27]. Pathologists will analyse as many nodes as possible in line with recent recommendations, with a minimum of 15 [27-31].

The trial compares regimens that have been already tested within randomised studies, and a knowledge and experience of these approaches has been established in the participating centres. This includes the MAGIC regimen, initially designed for gastric cancer and increasingly applied to junctional tumours, and the recently reported CROSS trial data. The trial design group and the disease-specific sub group in Cancer Trials Ireland consider that sufficient gaps exist in the evidence-base at this time with respect to the optimum approach to adenocarcinoma of the oesophagus and junction to justify this comparison, in particular it addresses the added value if any of radiation therapy. The MAGIC study included a minority of patients with oesophageal and junctional tumours, and staging and quality assurance modalities did not encompass current standards. The CROSS trial did not include PET in staging, excluded type III junctional tumours, and included a mix of pathological subtypes. The FLOT4 Trial was not powered for OGJ adenocarcinoma and the surgical approaches utilised were those for stomach cancer.

The trial is unique in evaluating two established regimens (neoadjuvant and adjuvant chemotherapy vs. neoadjuvant chemoradiation) using modern staging, and strict surgical and pathological standards. One other trial compared broadly similar regimens but was stopped prematurely due to poor accrual[32]. The added value of the proposed trial includes the evaluation of health related quality of life (HRQL), a comparison of in-hospital postoperative complications, and the opportunity to collect tissue and blood samples for storage in a biobank for future research (Irish sites only).

Table 1: Randomised Trials of Neoadjuvant Chemotherapy versus Surgery

Trial, Year	Chemotherapy Regimen	Tumour Type	Sample Size	Primary Outcome
MAGIC, 2006	3 Cycles: Cisplatin, 5-fluorouracil, Epirubicin	Adenocarcinoma	503*	Prolonged survival in chemotherapy arm at 5 years
Intergroup, 1998	3 Cycles: Cisplatin, 5-fluorouracil pre-and post	SCC and Adenocarcinoma	467	No difference in overall survival
FNCLCC/FFCD, 2011	2-4 Cycles: Cisplatin, 5-fluorouracil pre and post	Adenocarcinoma	224	Significantly improved overall survival and disease-free survival at 5 years
MRC, 2002	2 Cycles: Cisplatin, 5-fluorouracil	SCC and Adenocarcinoma	802	Prolonged survival in chemotherapy arm at 2 years
FLOT4, 2017	ECF/ECX v FLOT	Resectable gastric and OGJ adenocarcinoma	716	Significantly improved progression-free survival and overall survival

*14% of 503 had tumours of the lower oesophagus

Table 2: Randomised Trials of Neoadjuvant Chemo Radiotherapy versus Surgery

Author, Year	Chemotherapy Regimen	Radiotherapy Regimen	Concurrent or Sequential	Tumour Type	Sample Size	Primary Outcome
Burmeister, 2005	1 Cycle: Cisplatin, 5-fluorouracil	35 Gy, 2.3 Gy/fraction	Concurrent	SCC and Adenocarcinoma	256	No difference In overall survival
Tepper, 2008	2 Cycles: Cisplatin, 5-fluorouracil	50.4 Gy, 1.8 Gy/fraction	Concurrent	SCC and Adenocarcinoma	56	Prolonged survival in chemo radiotherapy arm at 5 years
Urba, 2001	2 cycles: Cisplatin, 5-fluorouracil, Vinblastine	45 Gy, 1.5 Gy/fraction	Concurrent	SCC and Adenocarcinoma	100	No difference in overall survival
Walsh, 1996	2 cycles: Cisplatin, 5-fluorouracil	40 Gy, 2.7 Gy/fraction	Concurrent	Adenocarcinoma	113	Prolonged survival in chemo radiotherapy arm at 3 years
CROSS, 2010	5 weeks paclitaxel and carboplatin AUC=2	41.4 Gy 23 fractions	Concurrent	SCC and Adenocarcinoma	363	Prolonged survival in Chemoradiation group

DRAFT

2.4 Summary of trial and rationale

The primary objective is to compare neoadjuvant and adjuvant chemotherapy (Investigator's choice modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction. The MAGIC study included a minority of patients with oesophageal and junctional tumours and staging and Quality Assurance (QA) modalities did not encompass current standards. The CROSS trial was not specific to adenocarcinoma, and compared a multimodal regimen to surgery alone. The FLOT4 trial included both patients with gastric and OGJ adenocarcinoma and had a different surgical management plan.

2.5 Name and Description of Investigational Product/Treatments: Dosage and Administration

Patients will be randomised to either Arm A [neoadjuvant and adjuvant chemotherapy - investigator's choice of modified MAGIC (ECF/ECX or EOF/EOX or FLOT) and surgery] or Arm B (CROSS protocol: neoadjuvant chemotherapy with radiation therapy and surgery).

Note:

Chemotherapy agents can be rounded up or down as per institutional practise (e.g.: epirubicin to nearest 2 mg, oxaliplatin to nearest 5 mg, 5-fluorouracil to nearest 5 mg, capecitabine as 150 mg and 500 mg tablets.)

Dose banding is permitted in the trial to a maximum of 6% variance from calculated dose.

2.5.1 Arm A - Modified MAGIC Chemotherapy Regimen

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

The drugs used in the modified MAGIC regimen include epirubicin, cisplatin or oxaliplatin and 5-fluorouracil/capecitabine (Table 3). Epirubicin, cisplatin or oxaliplatin are both given on day 1 of each cycle only (i.e. every 21 days). Each cycle of chemotherapy lasts 21 days/3 weeks. A +/- 1 to 4 calendar day delay for drug infusions is acceptable due to holidays or scheduling. The patient may receive 5-fluorouracil 200 mg/m^2/day as a continuous intravenous infusion OR capecitabine 625 mg/m^2 orally. If clinically indicated, capecitabine and 5-fluorouracil can be interchanged during cycle 1 to 6, for example, if the patient is unable to swallow capecitabine. The choice between administering cisplatin or oxaliplatin and 5-fluorouracil or capecitabine is at the discretion of the investigator. 5-fluorouracil/ capecitabine are given daily for duration of each cycle (i.e. for 9 weeks pre-surgery and for 9 weeks post-surgery).

Table 3: Arm A- Modified MAGIC Regimen

ECF/ECX or EOF/EOX			
Drug	**Dose**	**Administration**	**Days Given**
Epirubicin	50 mg/m^2	Slow IV push into the side arm of NaCl 0.9% drip	Day 1
Cisplatin with hydration - mannitol 10%*	60 mg/m^2 500 ml	Dilute in NaCl 0.9%. Administer over 2 hours. Infuse concurrently with cisplatin over 2 hours	Day 1
OR			
Oxaliplatin	130 mg/m^2	Dilute in Dextrose 5%. Administer over 2 hours	
5-fluorouracil	200 mg/m^2/ Day	Given at a dose of 200 mg/m^2/ day by continuous infusion every day for 21 days/3 weeks	Daily for 21 days/3 weeks
OR			
Capecitabine	625 mg/m^2 twice daily	Taken orally twice daily for 21 days	Daily for 21 days/3 weeks

All chemotherapy agents must be stored, prepared, and administered according to the manufacturer's SmPC.

Frequency of epirubicin and cisplatin/oxaliplatin: Day 1 of every 21-day cycle

Frequency of 5-fluorouracil/capecitabine: Every day continuously for 3 cycles pre-operatively and 3 cycles post-operatively

* ***Note: The use of mannitol and pre/post hydration will be carried out as per the institution's and local standard practice at the discretion of the treating physician, if different from the above guidelines.***

2.5.2 Arm A - FLOT Chemotherapy Regimen

The drugs used in the FLOT regimen include 5-Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel (Table 4). A maximum of 8 cycles of FLOT chemotherapy will be administered to patients in Arm A of the study consisting of 4 cycles of chemotherapy pre-surgery and a further 4 cycles of chemotherapy post-surgery. Each cycle of chemotherapy lasts 14 days/2 weeks. A +/- 1 to 4 calendar day delay for drug infusions is acceptable due to holidays or scheduling.

Table 4: Arm A- FLOT Regimen

Drug	**Dose**	**Administration details**	**Days given**
Docetaxel	50 mg/m²	Administer over 1 hour IV Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
Oxaliplatin*	85 mg/m²	Administer over 2 hours IV Dilute in glucose 5%	Day 1 of each cycle
Leucovorin*	200 mg/m²	Administer over 2 hours IV Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
5-fluorouracil	2600 mg/m²	Administer over IV 24 hours infusion Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
Dexamethasone o equivalent	8 mg	PO twice daily	Day before, day of and day after
	Or dose and administration per standard practice		
Frequency of FLOT: Every 14 days			

** Oxaliplatin administration must always precede the administration of 5-fluorouracil.*
** Oxaliplatin may be given at the same time as Leucovorin using a Y connector.*

All chemotherapy agents must be stored, prepared, and administered according to the manufacturer's SmPC.

Refer to *Section 6.1.2.2 FLOT Chemotherapy Regimen* for FLOT regime administration and premedication guidelines.

2.5.3 Arm B – CROSS protocol: Chemotherapy and Radiotherapy Regimen

Arm B consists of the CROSS protocol, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive 4 and a half weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive. The chemotherapy and radiotherapy will run concurrently over a 4 and a half -week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29.
A +/- 1 to 4 calendar day delay for drug infusions is acceptable due to holidays or scheduling.

The chemotherapy regimen consists of the following:

Table 5: Arm B: Multimodal Chemotherapy

Drug	Dose	Administration Details	Days Given
Dexamethasone or equivalent	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Chlorphenamine (Piriton) or equivalent	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Ranitidine (Zantac) or equivalent/alternative	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Paclitaxel	50 mg/ m^2	The total calculated dose of paclitaxel, will be infused over1 hour IV (PVC free).	Days 1, 8, 15, 22 and 29
Ondansetron or equivalent	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Carboplatin A Under Curve =2	As per Calculation	The total calculated dose of carboplatin, will be infused over 1 hour IV.	Days 1, 8, 15, 22 and 29

All chemotherapy agents must be stored prepared, and administered according to the manufacturer's SmPC.

The absolute dose of carboplatin will be calculated for the target Area Under the Curve (AUC) = 2 according to the Calvert formula with a maximum weekly dose of carboplatin of 300 mg.:

The absolute dose of carboplatin = (Target AUC) X (Glomerular Filtration Rate + 25)

Cockcroft/Gault formula to be used for GFR calculations:

$$= \frac{N\ (140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (micromol/L)}}$$

Where N = 1.04 for females, and 1.23 for males

2.6 Special Warnings/ Precautions for use and Undesirable Effects of treatment

The current versions of the Summary of Product Characteristics (SmPC) documents are to be used to assess the expectedness of the treatment in the study (Appendix G).

2.6.1 Epirubicin

2.6.1.1 Epirubicin Special Warnings and Special Precautions for use

Epirubicin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Please refer to the current manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.2 Cisplatin

2.6.2.1 Cisplatin: Special Warnings and Special Precautions for use

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Yellow fever vaccine is contraindicated in patients receiving treatment with Cisplatin.

Cisplatin is contraindicated in patients with significant hearing loss.

Please refer to the current approved manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.3 5-FU

2.6.3.1 5-FU Special Warnings and Special Precautions for use

It is recommended that 5-fluorouracil should only be given by, or under the strict supervision of a qualified physician who is conversant with the use of potent antimetabolites and has the facilities for regular monitoring of clinical, biochemical and haematological effects during and after administration. All patients should be admitted to hospital for initial treatment.

Patients who are receiving treatment with sorivudine or its chemical analogues, such as brivudine, must not be enrolled in this trial as treatment with 5-fluorouracil administration is contraindicated. There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of 5- fluorouracil therapy.

Treatment with 5-fluorouracil products is contraindicated in patients with known complete DPD deficiency. 5-fluorouracil must not be given to patients homozygotic for DPD. Patient with known DPD deficiency are excluded from the trial.

Please refer to the approved manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.4 Capecitabine

2.6.4.1 Capecitabine Special Warnings and Special Precautions for use

Patients who are receiving treatment with sorivudine or its chemical analogues, such as brivudine, must not be enrolled in this trial as treatment with capecitabine administration is contraindicated. There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.

Treatment with capecitabine products is contraindicated in patients with known complete DPD deficiency. Patient with known DPD deficiency are excluded from the trial.

Please refer to the current approved manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.5 Carboplatin

2.6.5.1 Carboplatin Special Warnings and Special Precautions for use

Warnings:
Carboplatin should be administered by individuals under the supervision of a qualified physician who is experienced in the use of anti-neoplastic therapy. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

Yellow fever vaccine is contraindicated in patients receiving treatment with Carboplatin.

Please refer to the current approved manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.6 Paclitaxel

2.6.6.1 Paclitaxel Special Warnings and Special Precautions for use

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. Patients must be pre-treated with corticosteroids, antihistamines and H2 antagonists.
Paclitaxel should be given before cisplatin when used in combination.

Please refer to the current approved manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.7 Oxaliplatin

2.6.7.1 Oxaliplatin Special Warnings and Special Precautions for use

Oxaliplatin should be used in specialized departments of oncology and administered under the supervision of an experienced oncologist.

Please refer to the current approved manufacturer Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.8 Leucovorin

2.6.8.1 Leucovorin Special Warnings and Special Precautions for use

Leucovorin should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Please refer to the current approved manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

2.6.9 Docetaxel

2.6.9.1 Docetaxel Special Warnings and Special Precautions for use

Docetaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. Patients must be pre-treated with corticosteroids. Refer to Section 6.1.2.2 FLOT Chemotherapy Regimen for FLOT regime administration and premedication guidelines

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis could develop at any time and could lead to death. Patients should be closely monitored for early manifestation of serious gastrointestinal toxicity.

Ventricular arrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with docetaxel in combination regimens including 5-fluorouracil.

Please refer to the current approved manufacturer's Summary of Product Characteristics (SmPC) for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the IMP.

3. Study Objectives

3.1 Primary Objective

To evaluate one, two and three year survival of patients treated with resection plus neoadjuvant and adjuvant chemotherapy versus resection plus neoadjuvant chemo radiotherapy.

3.2 Secondary Objective(s)

To evaluate the effect of both neoadjuvant regimens on: clinical and endoscopic response rate (in particular relief of dysphagia, improvement in HRQL and endoscopic regression), tumour regression grade, surgical resection rate (including resectability and pathologic R0 resection), post-operative pathology, disease-free survival, time to treatment failure, site of treatment failure, toxicity and post-operative complications.

3.3 Exploratory Objective(s)

The collection of blood and tissue samples for storage in the biobank for future research**.**

4. Study Design

This is a multicentre phase III open-labelled, randomised controlled trial. Eligible patients will be randomised in a 1:1 fashion between Arm A: neoadjuvant and adjuvant chemotherapy [Modified MAGIC regimen (**ECF/ECX or EOF/EOX**) or **FLOT**] and surgery or Arm B: neoadjuvant chemotherapy with radiation therapy (CROSS protocol) and surgery with a modernised design and delivery of radiation therapy.

4.1 Study Aim

The aim of this study is to compare neoadjuvant and adjuvant chemotherapy (Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction exclusively in patients defined as high-risk for relapse, and encompassing strict surgical quality assurance and quality of life assessment sooner. High-volume (i.e. >30 resections per year) centres or nationally designated oesophageal cancer surgery centres will participate. It is envisaged that medical and radiation oncologists in all centres will participate in the trial.

4.2 Definition of patient population

Patients presenting with newly diagnosed cancer of the oesophagus or oesophago-gastric junction, pre-treatment stage cT2-3, N0-3, M0 will be assessed for suitability for inclusion to this trial.

4.2.1 Number of patients and Estimated Study Duration

It is anticipated that 540 patients will be accrued to this study at participating study sites located in Ireland, United Kingdom, Denmark, France, Sweden and Netherlands. Taking into account the time required to obtain local approval and to initiate all participating centres, the study is expected to take approximately 10.5 years. Which is an accrual time of approximately 9 years and all patients will be followed-up until death or until the last patient has completed 18 months follow-up, whichever occurs earlier. In Ireland, the recruitment started in January 2013. Other EU centres started recruitment in February 2015.

4.2.2 Duration of patient participation

The duration of study treatment for each patient is expected to be 6-7 months for Arm A and 3-4 months for Arm B. Patients will be followed-up until death or until the last patient has completed 18 months follow-up, whichever occurs earlier.

4.3 Study Endpoints

4.3.1 Primary end point

The primary endpoint is overall survival which will be calculated from the date of randomization to the date of death from any cause. Patients lost to follow-up, or those with no death recorded on the day the database is frozen, will be censored on the date of last follow-up.

4.3.2 Secondary end points

The following are other end points to be evaluated in this study:

Clinical and Endoscopic response rate:

- **Response rate** in neoadjuvant regimens will be based on clinical parameters, in particular relief of dysphagia, improvement in HRQL and endoscopic regression. Quality of life will be evaluated using the EORTC QLQ C30 (Including EORTC QLQ-OES 18) questionnaire (Appendix E). Endoscopic regression will be graded according to criteria set out in Appendix L.
- **Tumour Regression Grade**: In patients treated with neo-adjuvant therapy, the extent of residual carcinoma in the oesophagectomy specimen will be assigned to one of five categories as per Mandard et al (See Appendix B). TRG1 represents a complete response (pCR); TRG2 represents rare residual cancer cells scattered throughout the fibrosis; TRG3 represents an increase in the number of residual cancer cells, but fibrosis still predominate, TRG4 represents residual cancer cells outgrowing fibrosis and TRG5 represents a complete absence of regression change.
- **Surgical resection rate**: This includes (i) Resectability at surgery and (ii) R Status at final pathology. Please note that the circumferential resection margins will be determined by both the residual tumour classification system outlined by the Royal College of Pathology (RCP) and the College of American Pathologists (CAP) (Appendix K - Please also note that in the electronic Case Report Form (eCRF) 'Distance of carcinoma to nearest circumferential margin (mm)' is required.
- **Pathologic assessment** is performed as per standard guidelines and is based on the UICC/TNM 7th edition (2010) (Appendix F).
- **Disease-free survival**
- **Time to treatment failure**
- **Site of treatment failure**
- **Toxicity and Post-operative Complications:** Toxicity of treatment will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (Appendices C and J). In cases where these criteria do not apply, intensity should be defined according to the general clinical description of grades as per CTCAE. All post-operative complications will be captured for up to 90 days after surgery and graded according to the Clavien-Dindo classification system and the Esophagectomy Complications Consensus Group (Appendix I).

4.4 Study Treatments: dosage and regimen

Patients will be randomised to either:

Arm A - Modified MAGIC regimen: 3 pre- and 3 post-operative cycles of chemotherapy (each cycle lasts 21 days)

or;

- FLOT regimen: 4 pre- and 4 post-operative cycles of chemotherapy (each cycle lasts 14 days)

** The choice between administering MAGIC (ECF/ECX or EOF/EOX) or FLOT is at the discretion of the investigator.*

OR

Arm B - CROSS multimodality protocol of 5 weekly cycles of chemotherapy and 4 and a half weeks of radiation therapy.

Randomised patients are not permitted to cross over to the other arm within any study. Patients will be assigned by registration to one of two treatment arms in a 1:1 ratio. See Study Schema diagram in Section 4.7.

4.5 Description of dosage form, packaging and labelling of Investigational Product

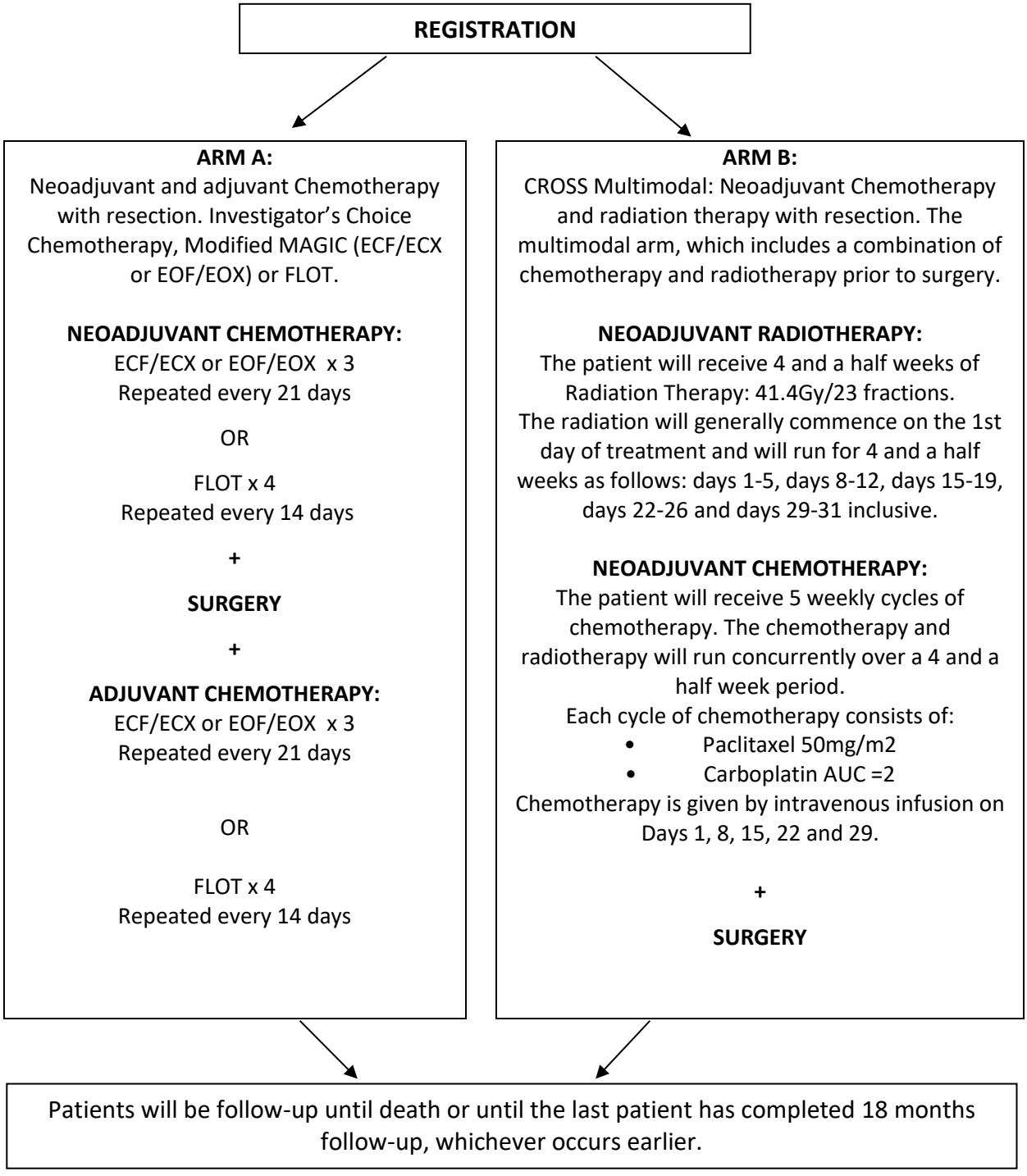
All study drugs will be obtained from commercial sources as open-label stock. The study drugs will not be provided or reimbursed by the Cancer Trials Ireland, the study Sponsor. Both the box label and vial label will fulfil all requirements specified by governing regulations.

4.6 Drug accountability procedures

All drugs used in this study will be commercial stock and will be sourced through the local hospital. All study drugs will be stored as per the current version of the products' SmPC (Summary of Product Characteristics) and the standard hospital procedures. Pharmacy will maintain dispensing records and temperature logs as per hospital pharmacy standard operating procedures.

Capecitabine prescriptions must be documented in the physician's order sheets or by retention of a copy of the prescription, if not dispensed directly by the hospital pharmacy. Compliance with capecitabine dosing will be assessed through questioning the patient during the visits and documented in the source documents.

4.7 Study Schema Diagram



4.8 Treatment Withdrawal

Study treatment may be discontinued according to patient wishes or if in the opinion of the treating clinician, the continued study treatment is not in the best interests of the patient. Wherever possible, patients should stay in the trial for study follow-up per protocol including scans and assessments until disease progression and followed up for survival thereafter. The primary reason for study treatment (including surgery) withdrawal and date of withdrawal should be recorded on the treatment withdrawal visit eCRF. The treatment withdrawal visit eCRF should be completed when any of the withdrawal criteria in sections 4.8.1 or 4.8.2.3 are met, regardless of whether the patient consents to be followed up or not as per the protocol.

4.8.1 Withdrawal Criteria

Criteria for which treatment will be withdrawn include:

- Treatment delays of more than two weeks are not permitted and may result in the patient being withdrawn from study treatment. The exceptions are:
    - Delays due to treatment related-toxicity, in which case a delay of up to 6 weeks is permitted before treatment is considered intolerable and the patient is withdrawn.
    - Other situations where a study treatment may need to be interrupted for clinical reasons.
    - However, if an interruption of study treatment of more than 3 weeks is anticipated, the study chief investigator should be notified in advance, and further advice sought with regards to the appropriateness of restarting study treatment.
- Disease progression before completion of study treatment.
- Withdrawal of consent for treatment and/or study participation.
- Unacceptable treatment-related toxicity or adverse events as judged by either the patient's treating physician or the Chief Investigator.
- Pregnancy.
- Patient non-compliance.
- Disease recurrence before completion of study treatment
- Investigator's decision to withdraw patient from study treatment. Refer to 4.8.2.3 for examples.
- Death
- Lost to Follow-up
- Patient has a DPD deficiency and has been randomised to a 5-fluorouracil or capecitabine containing arm. The treating investigator should remove the patient from study treatment in favour of an alternate standard of care regimen (e.g. non 5-fluorouracil/capecitabine regimen). The patient will be followed up for survival per Section 9.8 Survival Follow-up.
- Other reasons that need to be specified in the CRF.

Table 6: Timing of Withdrawal and Follow-up Schedule

1. Withdrawal from Study Treatment	**Follow-up schedule**
Treatment discontinued prior to starting neo-adjuvant treatment.	Complete the treatment withdrawal visit eCRF. Patients will proceed to survival follow up. Refer to section 9.8 for assessments required in survival follow up. Where possible, date of progression of disease and any new anti cancer treatment should be captured in the eCRF.
Treatment discontinued before completion of neo-adjuvant treatment. For reasons other than disease progression/recurrence.	Proceed to the end of neoadjuvant treatment visit, study surgery and continue the assessments, and procedures as per table 18, 19 or 20 according to treatment arm and regimen selected. Complete the treatment withdrawal visit eCRF
Treatment discontinued before completion of adjuvant treatment. For reasons other than disease progression/recurrence.	Proceed to the post treatment visit as per table 23 or 24 and continue with study assessments and procedures post-surgery as per table 21 and 22 assessments for disease recurrence as per table. Complete the treatment withdrawal visit eCRF
3. Patient unable for surgery	
Patient which in the opinion of the Investigator are unable for surgery. Refer to section 4.8.2.3 for examples.	Complete the treatment withdrawal visit eCRF. Patients unable for surgery will proceed to survival follow up. Refer to section 9.8 for assessments required in survival follow up. Where possible, date of progression of disease and any new anti cancer treatment should be captured in the eCRF.
4: Disease progression/recurrence	
The patient is discontinued from study treatment and study follow-up in the event of: • Disease progression • Disease recurrence	Proceed to survival follow up. Refer to section 9.8 for assessments required in survival follow up. Where possible, any new anti cancer treatment should be captured in the eCRF.

5. Withdrawal from study follow-up	
If a patient withdraws post treatment and/or in the study follow-up for reasons such as: • Investigator's decision to withdraw patient from study follow-up. Refer to 4.8.2.3 for examples. • Patient non-compliance. • Other reasons that need to be specified in the CRF.	Complete the Post Treatment/Follow up Withdrawal eCRF and proceed if possible to Survival Follow up. Where possible, date of progression of disease and any new anti-cancer treatment should be captured in the eCRF.
6. Completion of 5 years of study follow-up	
When a patient completes 5 years of standard follow-up	Complete the Post Treatment/Follow up Withdrawal eCRF and proceed to Survival Follow up. Where possible, date of progression of disease and any new anti-cancer treatment should be captured in the eCRF.
7. Withdrawal from study/Off Study	
In the event that no further follow up of the patient is required due to: • Completed the study as per protocol criteria. • Withdrawal of patient consent for study participation • Lost to follow up • Death • Other: Specify reason Early termination of the trial by the Sponsor	Document the reason why the patient is now off the study in the source notes and Off Study eCRF.
8. Consent Withdrawal	
The patient may withdraw consent to study treatment and/or study follow-up and/or survival follow-up at any time.	Refer to section 4.8.2.2 Patient Withdrawal Status.

4.8.2 Withdrawal Procedures

4.8.2.1 Criteria for Continuing Treatment

Study patients will be treated as per the trial regimens until disease progression or withdrawal from the study due to unacceptable toxicity or withdrawal of consent or other reasons listed in section 4.8.1 or 4.8.2.3. Throughout the study, patients will be evaluated for evidence of trial-drug-related toxicity. If a patient has an unacceptable toxicity, they must be withdrawn from trial treatment.

4.8.2.2 Patient Withdrawal Status

Even after a patient agrees to take part in this trial, the patient may withdraw from the trial at any time.

- **Study Follow-up:**
  If the patient decides to withdraw consent to trial treatment the patient should continue to be followed according to the trial follow-up schedule (All scans and assessments should be

completed per trial protocol) until disease progression and followed up for survival thereafter. The reason for withdrawal from trial treatment should be recorded on the Treatment withdrawal visit eCRF.
If a patient withdraws post treatment and/or in the trial follow-up, they should complete the Post Treatment/Follow up Withdrawal eCRF and proceed if possible to the Survival Follow up.

Refer to Table 21 and 22 for trial follow-up procedures

- **Survival Follow-up**:
  Alternatively, the patient may choose to withdraw consent to trial treatment and trial follow-up per protocol but consent to survival follow-up only.

  Patients will then be followed-up for survival until death or the end of the trial occurs, whichever occurs earlier. Survival follow up will occur every three months for the first year and then six monthly. Unless otherwise indicated, the survival follow-up may occur by telephone, and where possible, the following should be documented:
  - Progression of disease should be documented by appropriate imaging and biopsy if required.
  - Resolution of any treatment related toxicities due to treatment received within this trial, if ongoing at the time the patient was withdrawn from the trial.
  - Survival status. If a patient is lost to follow-up this should be documented and data reported on the eCRF
  - Any post-progression cancer treatment (treatments or regimens used) should be recorded on the Anti-Cancer Treatment eCRF.
  - Patients that are removed from the trial due to any reason (i.e., toxicity, delays, etc.) but still go on to continue standard trial (CROSS or MAGIC/FLOT) therapy off trial, should still have this information captured on the Anti-Cancer Treatment eCRF.

- **Off Study:**
  Alternatively, the patient may choose to withdraw consent to trial treatment and follow-up and have no further interaction regarding the trial. In this case, the investigator must provide Cancer Trials Ireland with written documentation of the patient's decision to fully withdraw from the trial. Withdrawal from trial should be recorded on the Off Study eCRF. The patients care will then be monitored/delivered as per standard care.

4.8.2.3 Investigator initiated discontinuation of trial therapy

The investigator may require a patient to discontinue trial treatment if one of the following occurs:
- The patient develops a serious side effect that he/she cannot tolerate or that cannot be controlled with other medications
- The patient's health gets worse
- The patient is unable to meet the trial requirements
- New information about the drug or other treatments for oesophageal cancer becomes available.
- Other reasons that need to be specified in the CRF.
- Patient non-compliance.

If trial treatment is stopped but the patient still allows the trial doctor to follow his/her care, the patient should continue to be followed according to the trial follow-up schedule, all scans and assessments should be completed per trial protocol until disease progression and followed up for survival thereafter.

In addition, the investigator may require a patient to discontinue trial treatment and trial follow-up if one of the following occurs:

- Surgical pathology shows poor prognostic features which in the opinion of the treating Investigator requires new anti-cancer treatment.
- Diagnosis of a new primary cancer which in the opinion of the treating Investigator requires new anti-cancer treatment. Please complete the New Primary Cancer eCRF.
- Patient unable for surgery. For example, a dose-related toxicity preventing surgery, or deteriorated performance status precluding surgery.
- Other reasons that need to be specified in the CRF.

Patients requiring new anti-cancer treatment or patients unable for surgery will proceed to survival follow up. Refer to section 9.8 for assessments required in survival follow up. Where possible, date of progression of disease and any new anti-cancer treatment should be captured in the eCRF.

4.8.3 Assessments at treatment withdrawal:

The following assessments should be performed whenever possible when a patient is withdrawn from treatment for any reason:

- Physical examination
- Clinical history update at day of withdrawal
- Blood tests as clinically indicated
- ECOG performance status (Appendix D)
- Other standard of care procedures, as deemed appropriate by the Principal Investigator.

The primary reason and date for a patient's withdrawal from the trial is to be recorded on the case report form.
Withdrawn patients who have received trial treatment will not be replaced.
In the event a patient is deemed ineligible after registration, the patient must be withdrawn from the trial before receiving the first dose of trial drug. These patients will be followed up for survival unless they elect to withdraw consent from the trial.
Further details on patient withdrawal can be found in section 9.7 Assessments required for patients with progression of disease (for both treatment arms).

5. Exploratory Study: Translational research – *for St James's Hospital, Dublin, Ireland Only*

5.1 Study background

The Translational Research study will be conducted exclusively at St. James's Hospital, Dublin, Ireland. All upper GI patients undergoing endoscopy or surgery at St. James' Hospital are invited to take part in the 'Establishment of an upper gastrointestinal (GI) biobank from patients undergoing endoscopy or surgery to study diseases of the upper GI tract' research study at SJH. At the time of enrolment into the main Neo-AEGIS study, patients who have consented to the SJH biobank study will be invited to consent to allow the linking of clinical data collected as part of the main Neo-AEGIS study with research carried out on their tissue and blood collected as part of the biobank study. Samples (tumour and/or normal tissue (pre and post-surgery) and blood samples) are collected in accordance with the upper GI biobank protocol, outlined in section 5.3 and 5.4 of the protocol. The aim of the upper GI biobank research study is to identify both tumour and circulating biomarkers and cellular and molecular signatures to increase knowledge of the cellular and molecular mechanism(s)/signatures underlying disease progression , disease recurrence and treatment response in oesophageal cancer and to facilitate the identification of biomarkers predicting patient response to treatment, disease progression and disease recurrence. All of this biological data will be correlated with detailed clinical,

pathological and patient outcome data. Some biobank studies involved national and international collaborators for which security measures linked to all samples are included.

5.2 Informed consent

Upon presentation for diagnostic workup, all oesophageal/OGJ cancer patients at St James's Hospital, Dublin, are invited to consent to having some of their tissue and blood taken for '*The Establishment of an Upper Gastrointestinal (oesophagus, stomach, pancreas) biobank from patients undergoing endoscopy or surgery to study diseases of the upper GI tract*' research study. These samples will be taken at the same time as biopsies for histological diagnosis, and at surgical resection.

Informed consent to participate in the upper GI biobank study will be obtained from patients by an authorised member of the biobank research team, prior to carrying out any sample collection procedures. Prior to signing the ethically approved upper GI biobank consent form, eligible patients will be provided with written information about the upper GI biobank study. They will be fully informed about the upper GI biobank study and will have ample time to consider their participation. At the time of consent to the main Neo-AEGIS study, the patient's permission will be sought to link information from analysis of samples with clinical data obtained from main Neo-AEGIS clinical study in the future. Patients who consent to the use of their information for this purpose will be asked to sign and date the Ethics Committee approved Neo-AEGIS Translational Study Patient Information Leaflet and Consent form.

5.3 Collection of diagnostic and resected oesophageal tissue – Upper GI biobank SJH

5.3.1 Fresh diagnostic tissue

In addition to the biopsies collected for routine diagnostic purposes, patients will be asked to consent to 6 additional oesophageal biopsies (tumour and normal) to be used for the upper GI biobank. Upon oesophagogastricduodenoscopy, the additional diagnostic biopsies taken for research will be placed into and wrapped in saline gauze in appropriately labelled 70ml sterile container. Samples are then further divided in labelled 2ml screw top tubes for long term storage. Specimens will be collected immediately by a member of the research team. These 6 biopsies will be used as follows: snap frozen in liquid nitrogen, placed in RNA*later* or used for explant culture. From snap frozen biopsies, the levels of DNA mutations gene and protein expressions will be assessed. For samples placed in RNA*later*, RNA will be extracted and used to assess small RNA and gene expression by microarray technology and quantitative PCR. Biopsies used for explant culture experiments will be cultured to produce conditioned media. This fresh explant tissue will be cut up into smaller pieces and either untreated or treated with X-ray radiation, chemotherapeutics, small molecules, antibodies or a combination. RNA, DNA and protein will be collected from these explant cultures by standard methods for future research studies. Conditioned media from explant culture will be assessed for protein secretions and the effect of the conditioned media on the biology of cancer cells and immune cells will also be assessed.

5.3.2 Fresh resected tissue

At the time of surgery, patients will be asked to consent to donate resected tissue to be used for the upper GI biobank. Surgical specimens from oesophageal cancer resections will be collected immediately after resection from the operating theatre by an member of the research team and will be transported in an unfixed state in a sterile closed container to the pathology department. Approximately 5 cm^3 of tumour tissue and corresponding non-neoplastic tissue (taken at least 5 cm from the tumour margin, where possible) is removed from the resected sample, divided into smaller fragments and either snap-frozen in liquid nitrogen, placed in RNA*later*, or used for explant culture. Resected tissue will only be taken in cases where there is enough material present, to ensure it will not compromise the subsequent histopathologic staging. From snap frozen biopsies, the levels of DNA mutations. For samples placed in RNA*later*, RNA will be extracted and used to assess small RNA and

gene expression by microarray technology and quantitative PCR. Tissue used for explant culture experiments to produce conditioned media. This fresh explant tissue will be cut up into smaller pieces and either untreated or treated with X-ray radiation, chemotherapeutics, small molecules, antibodies or a combination. RNA, DNA and protein will be collected from these explants cultures by standard methods for future research studies. Conditioned media from explant culture will be assessed for protein secretions and the effect of the conditioned media on the biology of cancer cells and immune cells will be assessed.

5.3.3 Formalin-fixed paraffin-embedded diagnostic and resected oesophageal tissue

In addition to fresh tissue, patients will also be asked to consent to the use of their formalin-fixed paraffin-embedded tumour tissue (both diagnostic and resected tissue) for the upper GI biobank, which is stored in the Pathology Department of St. James's Hospital. This tissue will be used for studies with RNA, tissue microarrays and immunohistochemistry analysis, to investigate the correlation of cellular and molecular biomarkers with response to treatment and other clinicopathological parameters. Cellular biochemistry profiles will also be assessed.

5.4 Collection of blood samples – Upper GI biobank SJH

Patients will be asked to consent to the collection of additional blood samples, both before and after treatment for the purpose of the upper GI biobank. Blood samples will be taken by a member of the biobank research team, ideally at the same time as other blood tests in order to avoid the need for an additional venesection. Approximately 20 mL of blood will be collected and then aliquoted into 2 tubes, one containing EDTA anticoagulant and one containing coagulant for serum. Blood will be collected using standard butterfly needles (vacutainer system or similar tubes are suitable) and as per standard hospital practice. DNA, RNA, protein and cellular fractions will be isolated from whole blood, plasma and serum specimens by standard methods. Whole blood, plasma and serum will be biobanked and assessed for the levels of circulating markers and immune cell profiles, which will then be correlated with response to treatment and other clinicopathological parameters.

5.5 Sample storage, data management and disposal

Samples will be identified in the biobank at SJH using study codes assigned to the patient only. It is possible for researchers to link the study codes to the unique trial number on the patient's consent form, but not to confidential patient information. Only the Principal Investigator and Research Team will have access to the identification of individual patients. The samples collected during the course of this study will be stored in the Dept. of Surgery, Trinity Translational Medicine Institute, St. James Hospital. Access to samples will only be permitted for ethically reviewed academic studies. Samples collected may be shared as part of collaborative research endeavours with other academic institutions, including overseas institutions, possibly including those outside the European Union and commercial biopharmaceutical companies. Where this occurs, the research proposed will be reviewed by the relevant Research Ethics Committee.

The upper GI biobank is designed to use clinical information collected as part of a normal clinical assessment of patients with these types of conditions. At all times during the data collection process, patient confidentiality will be maintained by ensuring only the patients unique trial number is placed on all documentation. The patient's name and personal identifiable information is retained only on the signed consent form which is kept in a locked office by the research coordinator. This identifiable information is also stored electronically on the Biobank Database which is a secure password protected file held on the SJH server, with restricted access.

Withdrawal from the Upper GI biobank / Neo-AEGIS Translational sub-study can be done at any time by contacting the hospital or research team. If a participant changes their mind, all remaining samples in storage at the time of consent withdrawal will be destroyed in the way human tissue and bloods

from hospitals are normally destroyed. Participants will be asked if data generated from samples up to the point of withdrawal can remain part of the study to ensure study integrity. No new data will be generated or held after consent withdrawal. If a participant so wishes, all data generated will be destroyed.

5.6 Translational contact points

All translational queries for this trial will be handled by the following:

Name	Phone	Email
Dr Jacintha O'Sullivan Senior Lecturer in Surgery/ Molecular Oncology, Department of Surgery, Trinity Translational Medicine Institute, Trinity Centre for Health Sciences, St James Hospital, Dublin 8	+353-1-8962149	osullij4@tcd.ie
Dr Niamh Lynam-Lennon / Dr Anshul Bhardwaj Research Assistant Professor / Biobank Manager Department of Surgery, Trinity Translational Medicine Institute Trinity Centre for Health Sciences, St James Hospital, Dublin 8	+353-1-896 1685 / +353-1-428 4343	lynamlen@tcd.ie / anshul.bhardwaj@tcd.ie

6. Study Treatment Regimens

6.1 Schedule, Route/mode of administration

6.1.1 Treatment Assignment/Treatment periods

Patients will be assigned by registration to one of two treatment arms in a 1:1 ratio. Patients randomised are not permitted to cross over to the other arm within the trial.

Patients will be randomised to either:

- Arm A: Neoadjuvant and adjuvant chemotherapy [Modified MAGIC (ECF/ECX or EOF/EOX) or FLOT chemotherapy regimen] and surgery
OR
- Arm B: Chemotherapy with radiation therapy (as per multimodal CROSS protocol) and surgery.

6.1.2 Arm A – Neoadjuvant and adjuvant chemotherapy and surgery

Decisions about which standard of care chemotherapy regimen to use i.e. Modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

6.1.2.1 Modified MAGIC Chemotherapy Regimen

A maximum of 6 cycles of **ECF/ECX or EOF/EOX** chemotherapy will be administered to patients in Arm A of the trial consisting of 3 cycles of chemotherapy pre-surgery and a further 3 cycles of chemotherapy post-surgery.

Each cycle of chemotherapy lasts 21 days/3 weeks. The drugs used in the modified MAGIC regimen include epirubicin, cisplatin or oxaliplatin and 5-fluorouracil IV/capecitabine PO. **The choice between**

administering cisplatin or oxaliplatin and 5-fluorouracil or capecitabine is at the discretion of the investigator. If clinically indicated, capecitabine and 5-fluorouracil can be interchangeable (see section 2.5.1). Epirubicin and cisplatin are both given intravenously on day 1 of each cycle only (i.e. every 21 days). A +/- 1 to 4 calendar day delay for drug infusions is acceptable due to holidays or scheduling. 5-fluorouracil is given by continuous intravenous infusion via a pump. Pump changes occur at day 1, day 8 and day 15 of each cycle. Alternatively, capecitabine is given orally every day for the duration of each cycle (i.e. for 9 weeks pre-surgery and for 9 weeks post-surgery).

ECF/ECX or EOF/EOX dosing will be based on the baseline body surface area (BSA). Weight will be measured at the beginning of each cycle. In cases where there is a ≥ 10% difference in weight compared to the previous weight used to calculate the dose, the dose should be recalculated using the new weight. Once the new dose is calculated, it can then be banded up to a 6% variance. If there is a <10% difference in weight, dosing is to be administered according to standard institutional practices.

Table 7: ARM A-Modified MAGIC Regimen

Drug	Dose	Administration details	Days given
Epirubicin	50 mg/m^2	Slow IV push into the side arm of NaCl 0.9% drip	Day 1 of each cycle
Cisplatin **with hydration - mannitol 10%*** **OR** **Oxaliplatin**	60 mg/m^2 50 0ml 130 mg/m^2	Dilute in NaCl 0.9%. Administer over 2hours. Infuse *concurrently* with cisplatin over 2 hours Dilute in Dextrose 5%. Administer over 2 hours	Day 1 of each cycle
5-fluorouracil **OR** **Capecitabine**	200 mg/m^2 625 mg/m^2	Given at a dose of 200mg/m^2 per day by continuous IV infusion for 3 cycles i.e. 9 weeks pre surgery and 9 weeks post-surgery 625 mg/m^2 orally twice daily for 3 cycles i.e. 9 weeks pre surgery and 9 weeks post-surgery	
Frequency of epirubicin, cisplatin or oxaliplatin: every 21 days			

All chemotherapy agents must be stored, prepared, and administered according to the manufacturer's SmPC.

Notes:

1. Epirubicin is an anthracycline with a maximum lifetime exposure. Ensure patient's previous cumulative exposure to all anthracyclines is less than the equivalent of 450 mg/m^2 of doxorubicin.
2. Capping of BSA is at the discretion of the investigator.
3. Adequate pre-and post- hydration is essential for cisplatin.
4. Hydration guidelines:
   ***Pre-hydration:** 1L NaCl 0.9% over 2 hours
   ***Post-hydration:**1L NaCl 0.9% with 40 mmol K^+ and 5 g $MgSO_4$ over 2 hours.

Note: The use of mannitol and pre/post hydration and antiemetics will be carried out as per the institution's and local standard practice at the discretion of the treating physician, if different from the above guidelines.

Table 8: Dose Calculation Table for Capecitabine

Single Dose (mg)	Number of tablets per dose	
	150mg	**500mg**
650	1	1
800	2	1
1000	0	2
1150	1	2
1300	2	2

6.1.2.2 FLOT Chemotherapy Regimen

A maximum of 8 cycles of **FLOT** chemotherapy will be administered to patients in Arm A of the trial consisting of 4 cycles of chemotherapy pre-surgery and a further 4 cycles of chemotherapy post-surgery. Each cycle of chemotherapy lasts 14 days/2 weeks. A +/- 1 to 4 calendar day delay for drug infusions is acceptable due to holidays or scheduling.

Table 9: ARM A- FLOT

Drug	Dose	Administration details	Days given
Docetaxel	50 mg/m²	Administer over 1 hour IV Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
Oxaliplatin*	85 mg/m²	Administer over 2 hours IV Dilute in glucose 5%	Day 1 of each cycle
Leucovorin*	200 mg/m²	Administer over 2 hours IV Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
5-fluorouracil	2600 mg/m²	Administer over IV 24 hours infusion Dilute in NaCl 0.9% or 5% glucose	Day 1 of each cycle
Dexamethasone o equivalent	8mg	PO twice daily	Day before, day of and day after
	Or dose and administration per standard practice		
Frequency of FLOT: Every 14 days			

***** *Oxaliplatin administration must always precede the administration of 5-fluorouracil.*
** Oxaliplatin may be given at the same time as Leucovorin using a Y connector.*

All chemotherapy agents must be stored, prepared, and administered according to the manufacturer's SmPC.

FLOT Pre-medications:
Dexamethasone (or equivalent) should be given to prevent fluid retention and allergic reactions e.g. Dexamethasone 8mg PO twice daily for 3 days can be administered, starting one day prior to each docetaxel administration, unless contraindicated. Alternatively, an equivalent dose and administration of steroids may be used per local standards.

The FLOT regime is assigned as a Moderate Emetogenic Risk. The use of antiemetics will be carried out as per the institution's and local standard practice at the discretion of the treating physician.

Medication may be required for management of diarrhoea. Diarrhoea management will be carried out as per local standard practice at the discretion of the treating physician. e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day).

Administration of FLOT chemotherapy regimen

FLOT dosing will be based on the baseline body surface area (BSA). Weight will be measured at the beginning of each cycle. In cases where there is a ≥ 10% difference in weight compared to the previous weight used to calculate the dose, the dose should be recalculated using the new weight. Once the new dose is calculated, it can then be banded up to a 6% variance. If there is a <10% difference in weight, dosing is to be administered according to standard institutional practices.

6.1.3 Arm B – Chemotherapy with radiation therapy and surgery

Arm B consists of the multimodal arm as per the CROSS protocol, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive **4 and a half weeks of radiation therapy (41.4 Gy/23 fractions) and 5 weekly cycles of chemotherapy.** The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive. Either 3-Dimensional Conformal Radiation Therapy (3D-CRT) or Intensity Modulated Radiation Therapy (IMRT) may be used. Bidaily RT (≥6 hours apart) is permitted at the discretion of the treating clinician. The patient will receive 5 cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. A +/- 1 to 4 calendar day delay for drug infusions are acceptable due to holidays or scheduling. Institutional standard practice may be followed regarding the length of time between administration of radiation therapy and chemotherapy. Please refer to RT Planning Guidance Document for guidelines on fractionation. The chemotherapy drugs used in the multi-modal regimen include paclitaxel and carboplatin given intravenously. The absolute dose of carboplatin will be calculated for the target AUC=2 according to the Calvert formula:

The absolute dose of carboplatin = (Target AUC) X (Glomerular Filtration Rate + 25)

Cockcroft/Gault formula to be used for GFR calculations:

$$= \frac{N\ (140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (micromol/L)}}$$

Where N = 1.04 for females, and 1.23 for males

Calculated Creatinine Clearance should be capped at 125 mL/min when used to calculate the initial dose of carboplatin using the Calvert Formula, with a maximum weekly dose of carboplatin of 300 mg.

Weight will be measured and creatinine clearance should be calculated before each weekly dose of carboplatin. In cases where there is a ≥ 10% difference in weight compared to the previous weight used to calculate the dose, the dose should be recalculated using the new weight. Once the new dose is calculated, it can then be banded up to a 6% variance. If there is a <10% difference in weight the dosing of carboplatin should follow standard institutional practices. Lean or ideal body weight may be used for the GFR calculation using the Cockcroft Gault formula to compensate for the over estimation of CrCl in certain conditions (e.g., muscle wasting, obesity, ascites).

Paclitaxel dosing will be based on the baseline body surface area. Weight will be measured at the beginning of each cycle. In cases where there is a ≥ 10% difference in weight compared to the previous weight used to calculate the dose, the dose should be recalculated using the new weight. Once the new dose is calculated, it can then be banded up to a 6% variance. If there is a <10% difference in weight, dosing is to be administered according to standard institutional practices.

Table 10: ARM B - CROSS Multimodal Chemotherapy Protocol

Drug	Dose	Administration Details	Days Given
Dexamethasone or equivalent	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Chlorphenamine (Piriton) or equivalent	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Ranitidine (Zantac) or equivalent/ alternative	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Paclitaxel	50 mg/ m^2	The total calculated dose of paclitaxel, will be infused over 1 hour IV.	Days 1, 8, 15, 22 and 29
Ondansetron or equivalent	Dose and administration per local standard practice		Days 1, 8, 15, 22 and 29
Carboplatin AUC=2	As per calculation	The total calculated dose of carboplatin, will be infused over 1 hour IV.	Days 1, 8, 15, 22 and 29

All chemotherapy agents be stored, prepared, and administered according to the manufacturer's SmPC.

6.2 Radiotherapy Trials Quality Assurance (RTTQA)

All centres who wish to participate in this trial must satisfactorily complete two pre-accrual outlining benchmark cases consisting of one mid and one lower oesophageal cancer case. Outlines will be compared against a consensus reference volume (gold standard) derived from the outlines of Radiation Oncology Trial Management Group members.
One pre-outlined patient per centre must be planned by each participating radiotherapy centre. Centres that wish to treat Neo-AEGIS CROSS patients with 3D CRT only should submit a 3D CRT plan only. Centres that wish to treat Neo-AEGIS CROSS patients with IMRT only should submit an IMRT plan only. Centres that wish to use both techniques should submit both a 3D CRT and an IMRT plan. Patients treated with IMRT must be planned using 4-Dimensional CT (4DCT). A Plan Assessment Form (PAF) should be completed and submitted at the same time (UK only - access via RT National Lead for the UK). A Radiotherapy Process Document – in line with which all trial patients will be scanned, planned and treated- must be produced by each participating radiotherapy centre.

'On-trial' QA: Patients are required to commence radiotherapy within 21 calendar days of registration meaning that prospective/real-time review is not practical. Instead, there will be *timely-retrospective* review of the outline and plan for the first patient case from each centre. A second case will also be reviewed, should there have been an issue with the first case. Furthermore, a random allocation of 10% of all outlines and plans will be submitted from all centres for timely-retrospective review as above.

Key criteria will include:

- Radiotherapy will be administered via single phase 3D CRT or IMRT plan. The dose will be prescribed and recorded as per International Commission on Radiation Units and Measurements (ICRU) 50/62. Intravenous contrast is mandatory unless medically contradicted.
- **The use of cone beam CT matched to planning CT scans is mandatory within this study, though exceptions will be permitted if discussed and approved with the National Radiotherapy Principal Investigator.**

Radiotherapy data collection is performed via the Case Report Forms. This includes planning data and dose to PTV and OARs. eCRF data will be collected to ensure compliance with the Radiotherapy Process and QA procedures.

Detailed description of the radiotherapy process and QA procedures is available in the 'Radiotherapy Treatment Planning and Delivery' document developed and approved for this trial.

6.3 Packaging and Labelling

Please refer to section 4.5 Description of dosage form, packaging and labelling of Investigational Product.

6.4 Concomitant medications

During the course of the trial, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those contraindicated in the SmPC for each trial drug. The current versions of the summary of product characteristics (SmPC) documents listed in Appendix G are to be used to assess the expectedness of the serious adverse reactions (SARs) to the IMPs in the trial. Antiemetic's will be administered as per ASCO Antiemetic guidelines for both Arm A and Arm B (Appendix H). Prophylactic treatments also constitute concomitant medications and should therefore be captured on the eCRF.

Concomitant medications should be documented from informed consent until 30 days post-last dose of neo-adjuvant treatment and again from the first cycle of adjuvant chemotherapy until 30 days post-last dose of adjuvant treatment. Medications for adverse events and serious adverse events should be recorded in the eCRF for up to 30 days post-last chemotherapy treatment.

6.5 Permitted medications/treatments

- Any form of pain medication.
- Steroids for symptomatic treatment of tumour cachexia.
- Growth factors (G-CSF or GM-CSF) may be used for prophylaxis or to treat the myelosuppressive effects of chemotherapy according to local treatment policy.
- Emergency or elective surgery or procedures for the management of tumour related symptoms or complications, such as tumour related bleeding or bowel obstruction, are permitted. Study treatment should be interrupted during the perioperative period. If the course of trial treatment has not been completed, and if clinically appropriate to do so (i.e. In the absence of worsening symptoms due to tumour progression on treatment), trial treatment may be recommenced after the patient is appropriately recovered from the procedure. For example, a minimum of 6 weeks may be required after major surgery, whereas no break may be required for minor procedures such as the insertion of lines, percutaneous feeding tubes or stents).
- Emergency or elective surgery for the insertion of lines for delivery of treatment, or the management of line related complications, is permitted.
- Emergency surgery for the management of non-gastro-oesophageal cancer or treatment related reasons are permitted if clinically appropriate. Study treatment may require interruption, as above.

Any surgery or radiotherapy should be documented in the appropriate eCRF page. Any concomitant medication associated with an adverse event should be documented and collected on the eCRF.

6.6. Dose Modification and Delay Instructions

Please refer to the guidelines provided in this section for dosing. Further information on dose delays can also be found in section 4.8.1 Withdrawal Criteria.

6.6.1 Dose Modifications for Arm A- Modified MAGIC Regimen

6.6.1.1 ECX Regimens dose modification, delay and stopping instructions

Table 11: Dose Modifications for Arm A - ECX

Haematology			
ANC (x10^9/L)		**Platelets (x10^9/L)**	**Dose**
Greater than or equal to 1.5	and	Greater than 100	100%
0.5 to less than 1.5	or	50 to less than 100	Delay treatment until recovery then 100%
Less than 0.5	or	Less than 50	Delay treatment until recovery and reduce epirubicin, cisplatin, and capecitabine by 25% for subsequent cycles
Febrile Neutropenia			Delay treatment until recovery and reduce epirubicin, cisplatin, and capecitabine by 25% for subsequent cycles

Hand-Foot Skin Reaction: for Capecitabine					
Grade	**Hand-Foot Skin Reaction**	**1st Event Dose**	**2nd Event Dose**	**3rd Event Dose**	**4th Event Dose**
1	Skin changes (e.g. numbness, dysesthesia, paraesthesia, tingling, erythema) with discomfort not disrupting normal activities	100%	100%	100%	100%
2	Skin changes (e.g. erythema, swelling) with pain affecting activities of daily living	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
3	Severe skin changes (e.g. moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Delay* then 75%	Discontinue or delay* then 50%	Discontinue	Discontinue
**Stop treatment immediately and delay until resolved to grade 0-1*					

Other Non-Haematologic Toxicity: for Capecitabine		
Toxicity Criteria		
Grade	**Diarrhoea**	**Nausea and Vomiting**
0-1	Increase of 2-3 stools/day or nocturnal stools	1 vomit/day but can eat
2	Increase of 4-6 stools/day or nocturnal stools	2-5 vomits/day; intake decreased but can eat
3	Increase of 7-9 stools/day or incontinence, malabsorption	6-10 vomits/day and cannot eat
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support; dehydration	10 vomits or more per day or requires parenteral support; dehydration

Other Non-Haematologic Toxicity Grade	**1st Event Dose**	**2nd Event Dose**	**3rd Event Dose**	**4th Event Dose**
0-1	100%	100%	100%	100%
2	Delay* then 100%	Delay* then 75%	Delay then 50%	Discontinue
3	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
4	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue
**Stop treatment immediately and delay until toxicity resolved to grade 0-1*				

Renal Impairment	
Calculated Cr Clearance (mL/min) by Cockcroft/Gault formula	**Cisplatin and capecitabine dose**
50 to 60	Reduce cisplatin by 25%
30 to less than 50	Reduce capecitabine by 25% and cisplatin by 50%
Less than 30	Withhold chemotherapy

Ototoxicity / Hearing impairment:
For patients with hearing impaired adverse event ≥ grade 1 and/or tinnitus or other 'ear and labyrinth disorder' ≥ grade 2, cisplatin may be switched to oxaliplatin following discussion with the sponsor/CI (on a per patient basis).

Hepatic Dysfunction: Dose modification may be required. Capecitabine has not been studied in severe hepatic dysfunction	
Hepatic Dysfunction Grade*	**Dose**
Mild	Reduce epirubicin by 25%
Moderate	Reduce capecitabine by 25% and epirubicin by 50%
Severe	Reduce capecitabine by 50% and omit epirubicin or withhold treatment
Treatment related Grade 3 or 4 Hyperbilirubinaemia	Delay treatment until toxicity resolves to Grade 2 or less

Refer to Appendix O: Classification for Hepatic Dysfunction* **Hepatic Dysfunction

Peripheral Neuropathy	
Grade	**Dose**
Grade 2 which is present at the start of the next cycle	Reduce cisplatin by 25%, if persists, reduce cisplatin by 50%
Grade 3 or Grade 4	Omit cisplatin

Mucositis and Stomatitis					
Grade	Mucositis and Stomatitis	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
2	Painful erythema, oedema, or ulcers but can eat	Delay* then 100%	Delay* then 75% for epirubicin, cisplatin, capecitabine	Delay* then 50% for epirubicin, cisplatin, capecitabine	Omit epirubicin, cisplatin, capecitabine
3 Or 4	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Delay then 50% epirubicin, cisplatin, capecitabine	Omit epirubicin, cisplatin, capecitabine		
Stop treatment immediately and delay until resolved to grade 0-1					

PRECAUTIONS:

1. Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to local institutional guidelines for treatment of same. Refer to above Table 11: Dose Modifications for Arm A: ECX for dose modifications. Once the dose is reduced for toxicity, it must not be subsequently escalated.

2. Renal toxicity: Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside

3. Ototoxicity and sensory neural damage should be assessed by history prior to each cycle.

4. Cardiac toxicity: Clinical cardiac assessment is required prior to epirubicin if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO).

5. Myocardial ischemia and angina occurs rarely in patients receiving capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment.

6. Extravasation: Epirubicin causes pain and tissue necrosis if extravasated. Refer to local institutional guidelines for treatment of same.

7. Dihydropyrimidine dehydrogenase (DPD)
Treatment with capecitabine products is contraindicated in patients with known complete DPD deficiency. Patient with known DPD deficiency are excluded from the trial.

Routine DPD testing is not standard across all hospitals. Pre- capecitabine testing for DPD deficiency is recommended, but not mandated by the protocol. DPD deficiency testing should be performed as per local site policy.

In the event that a DPD deficiency is identified post randomisation and the patient has been randomised to a 5-fluorouracil or capecitabine containing arm, the treating investigator should remove the patient from study treatment in favour of an alternate standard of care regimen (e.g. non 5-fluorouracil/capecitabine regimen). The patient will be followed up for survival per Section 9.8 Survival Follow-up.

Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with 5-fluorouracil or capecitabine. DPD deficiency may result in severe and unexpected toxicity– stomatitis, mucositis, diarrhoea, neutropenia, and neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. Capecitabine/5-fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhoea.

8. Possible drug interactions with capecitabine and warfarin, phenytoin and fosphenytoin have been reported and may occur at any time. Close monitoring is recommended (e.g., for warfarin, monitor international normalised ratio (INR) weekly during capecitabine therapy and for 1 month after stopping capecitabine).

6.6.1.2 ECF Regimens dose modification, delay and stopping instructions

Table 12: Dose Modifications for Arm A- ECF

Haematology			
ANC (x10^9/L)		**Platelets (x10^9/L)**	**Dose**
≥ 1	and	≥ 100	100%
0.5 to < 1	or	50 to < 100	Delay treatment until recovery Then 100%
< 0.5	or	< 50	Delay treatment until recovery and reduce epirubicin, cisplatin, and 5-fluorouracil by 25% for subsequent cycles
Febrile Neutropenia			Delay treatment until recovery and reduce epirubicin, cisplatin, and 5-fluorouracil by 25% for subsequent cycles
During weekly 5-fluorouracil treatment			
ANC (x10^9/L)		**Platelets (x10^9/L)**	**Dose**
0.5 – 1	Or	10-50	75%
Less than 0.5	Or	Less than 10	Hold
Weekly 5-fluorouracil infusion dose should be decreased to 75% if an episode of febrile neutropenia occurs with the prior cycle of treatment			

Renal Impairment	
Calculated Cr Clearance (mL/min) by Cockcroft/Gault formula	**Cisplatin and 5-fluorouracil dose**
50 to 60	Reduce cisplatin by 25%
30 to 50	Reduce 5-fluorouracil by 25% and cisplatin by 50%
Less than 30	Reduce 5-fluorouracil by 50% and omit cisplatin or withhold chemotherapy

Hepatic Impairment	
Hepatic Dysfunction Grade*	**Dose**
Mild	Reduce epirubicin by 25%
Moderate	Reduce 5-fluorouracil by 25% and epirubicin by 50%
Severe	Reduce 5-fluorouracil by 50% and omit epirubicin

**Refer to Appendix O: Classification for Hepatic Dysfunction*

Gastrointestinal – for 5-fluorouracil					
Grade	**Diarrhoea**	**1st Event Dose**	**2nd Event Dose**	**3rd Event Dose**	**4th Event Dose**
2	Increase of 4-6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output	Delay* then 100%	Delay* then 75%	Delay* then 50%	Omit 5-fluorouracil
3 Or 4	Increase of greater than 7 stools/day or grossly bloody diarrhoea, or incontinence, malabsorption; or severe increase in loose watery colostomy output requiring parenteral support	Delay* then 50 %	Omit 5-fluorouracil		
**Stop treatment immediately and delay until resolved to grade 0-1*					

Mucositis and Stomatitis – for 5-fluorouracil					
Grade	**Mucositis and Stomatitis**	**1st Event Dose**	**2nd Event Dose**	**3rd Event Dose**	**4th Event Dose**
2	Painful erythema, oedema, or ulcers but can eat	Delay* then 100%	Delay* then 75%	Delay* then 50%	Omit 5-fluorouracil
3 or 4	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Delay* then 50 %	Omit 5-fluorouracil		
**Stop treatment immediately and delay until resolved to grade 0-1*					

Hand-Foot Skin Reaction: for 5-fluorouracil					
Grade	**Hand-Foot Skin Reaction**	**1st Event Dose**	**2nd Event Dose**	**3rd Event Dose**	**4th Event Dose**
1	Skin changes (e.g., numbness, dysesthesia, paraesthesia, tingling, erythema) with discomfort not disrupting normal activities	100%	100%	100%	100%
2	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
3	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Delay* then 50%	Discontinue		
**Stop treatment immediately and delay until resolved to grade 0-1*					

Peripheral Neuropathy	
Peripheral Neuropathy Grade	**Dose**
Grade 2 which is present at the start of the next cycle	Reduce cisplatin by 25%, if persists, then reduce cisplatin by 50%
Grade 3 or Grade 4	Omit cisplatin

PRECAUTIONS:

1. Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to local institutional guidelines for treatment of same. Refer to above Table 12: Dose Modifications for Arm A: ECF for dose modifications. Once the dose is reduced for toxicity, it must not be subsequently escalated.

2. Renal toxicity: Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.

3. Ototoxicity and sensory neural damage should be assessed by history prior to each cycle.

4. Cardiac toxicity: Clinical cardiac assessment is required prior to epirubicin if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO).

5. Myocardial ischemia and angina occurs rarely in patients receiving 5-fluorouracil. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment.

6. Extravasation: Epirubicin causes pain and tissue necrosis if extravasated. Refer to local institutional guidelines for treatment of same.

7. Dihydropyrimidine dehydrogenase (DPD)
Treatment with 5-fluorouracil products is contraindicated in patients with known complete DPD deficiency. 5-fluorouracil must not be given to patients homozygotic for DPD. Patient with known DPD deficiency are excluded from the trial.
Routine DPD testing is not standard across all hospitals. Pre- 5-fluorouracil testing for DPD deficiency is recommended, but not mandated by the protocol. DPD deficiency testing should be performed as per local site policy.

Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with 5-fluorouracil or capecitabine. In the event that a DPD deficiency is identified post randomisation and the patient has been randomised to a 5-fluorouracil or capecitabine containing arm, the treating investigator should remove the patient from study treatment in favour of an alternate standard of care regimen (e.g. non 5-fluorouracil/capecitabine regimen). The patient will be followed up for survival per Section 9.8 Survival Follow-up.

Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with 5-fluorouracil or capecitabine. DPD deficiency may result in severe and unexpected toxicity – stomatitis, mucositis diarrhoea, neutropenia, and neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. 5-fluorouracil and capecitabine should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhoea.

8. Possible interactions with warfarin, phenytoin and fosphenytoin have been reported with 5-fluorouracil/capecitabine and may occur at any time. Close monitoring is recommended (e.g., for warfarin, monitor INR weekly during 5-fluorouracil/capecitabine therapy and for 1 month after stopping 5-fluorouracil/capecitabine).

6.6.1.3 EOF/EOX Regimens dose modification, delay and stopping instructions

This section provides dose modification instructions related for EOF/EOX Regimens related toxicities[35].

Table 13: Dose modification for Arm A-EOF/EOX

Dose Modifications for Neurologic Toxicity

Peripheral Neuropathy Grade*	**Dose Modification of oxaliplatin**
Grade 1	Maintain dose
Grade 2 paraesthesia persisting until next cycle	Reduce dose to 100 mg/m^2
Grade 3: paraesthesia > 7 days but resolved before next cycle paraesthesia persisting until next cycle	 Reduce dose to 100 mg/m^2 Discontinue oxaliplatin
Grade 4 of any duration	Discontinue oxaliplatin
Pharyngo-laryngeal (see precautions)**	Increase duration of infusion to 6 hours

***** Usually, discontinuation will be permanently. Nevertheless, administration of oxaliplatin can be resumed (e.g. after complete recovery from the related symptoms) if the investigator decides that this is in the best interest of the patient and does not expect the toxicity to reoccur.*

****** Pharyngo-laryngeal dysesthesia (investigator discretion used for grading):** Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe*

Dose Modifications for Renal Toxicity

Creatinine Clearance mL/min	**Oxaliplatin Dose**	**Capecitabine Dose**	**Epirubicin Dose**	**5-FU Dose**
Greater than 50	Continue Therapy	100%	Dose reduce in severe impairment only. Clinical decision	Dose reduce in severe impairment only. Clinical decision
30 to 50	Continue Therapy	75%		
Less than 30	Discontinue Therapy	Discontinue Therapy		

Dose Modifications for Hepatic Toxicity

Oxaliplatin Dose	**Capecitabine Dose**	**Epirubicin Dose**	**5-FU Dose**
Little information available. Probably no dose reduction necessary. Clinical decision.	Mild: 100% Moderate: 75% Severe: 50%.	Mild: reduce by 25% Moderate: reduce by 50% Severe: omit	Clinical decision. Moderate: reduce by 33.33% Severe: reduce by 50%

**Refer to Appendix O: Classification for Hepatic Dysfunction*

Dose Modifications Haematologic Toxicity

ANC		**Platelets**	**Dose modification epirubicin and oxaliplatin**
≥ 1.0 x 10^9/L	And	> 75 x 10^9/L	100%
0.5-0.99 x 10^9/L	or	50-74.9 x 10^9/L	Delay until recovery and reduce epirubicin next cycle by 25% and oxaliplatin to 100mg/m2
< 0.5 x 10^9/L	or	25-49.9 x 10^9/L	Delay until recovery and reduce epirubicin next cycle by 50% and oxaliplatin to 100mg/m2
		<25 x 10^9/L	Delay treatment until platelets recover to >75. Omit epirubicin from subsequent cycles and reduce oxaliplatin to 100mg/m2

ANC		Platelets	Dose modification Capecitabine			
			1st Event	2nd Event	3rd Event	4th Event
≥ 1.5 x 10^9/L	And	> 75 x 10^9/L	100%	100%	100%	100%
1-1.49 x 10^9/L	or	50 – 74.9 x 10^9/L	Delay until recovery then 100%	Delay until recovery then 75%	Delay until recovery then 50%	Discontinue
<0.5-0.99 x 10^9/L	or	25-49 x 10^9/L	Delay until recovery then 75%	Delay until recovery then 50%	Discontinue	Discontinue
<0.5 x 10^9/L		<25 x 10^9/L	Delay until recovery then 50%	Discontinue	Discontinue	Discontinue

Dose Modifications Hand and Foot Syndrome Toxicity

Hand-Foot syndrome		Dose modification 5-FU	Dose modification Capecitabine
Grade 1	Skin changes or dermatitis without pain e.g. erythema, peeling	Maintain dose	Maintain dose
Grade 2	Skin changes with pain not interfering with function	75% until resolved then consider increasing dose by 10%	Withhold Capecitabine until event resolves or decreases in intensity to grade 1.
Grade 3	Skin changes with pain, interfering with function	Delay until resolved then resume at 75%	Withhold Capecitabine until event resolves or ≤ grade 1. Subsequent doses of capecitabine should be decreased

Dose Modifications for 5-FU

Diarrhoea		Dose modification 5-FU
Grade 1	Increase of 2-3 stools/day or nocturnal stools; or moderate increase in loose watery colostomy output	Maintain dose
Grade 2	Increase of 4-6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output	75%
Grade 3	Increase of greater than 7 stools/day or grossly bloody diarrhoea, or incontinence, malabsorption; or severe increase in loose watery colostomy output requiring parenteral support	Discontinue or delay until toxicity resolved then resume at 50%
Stomatitis		**Dose modification 5-FU**
Grade 1	Painless ulcers, erythema or mild soreness	Maintain dose
Grade 2	Painful erythema, oedema, or ulcers but can eat.	75%
Grade 3	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Discontinue or delay until toxicity resolved then resume at 50%

Dose Modifications for Capecitabine (For toxicities other than haematologic, renal, hepatic and neurologic)

Toxicity Grade	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose
Grade 2 1st appearance 2nd appearance 3rd appearance 4th appearance	Interrupt until resolved to grade 0-1	 100% 75% 50% Discontinue permanently
Grade 3 1st appearance 2nd appearance 3rd appearance	Interrupt until resolved to grade 0-1	 75% 50% Discontinue permanently
Grade 4 1st appearance 2nd appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	 50% Discontinue permanently

PRECAUTIONS for Oxaliplatin and Capecitabine use:

1. Platinum hypersensitivity can cause dyspnoea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see table below) For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity pre-medication:

45 minutes prior to oxaliplatin:

- dexamethasone 20 mg IV or equivalent

30 minutes prior to oxaliplatin:

- Chlorphenamine 10 mg IV and ranitidine 50 mg IV or equivalent/alternative

2. Laryngo-pharyngeal dysesthesia is an unusual dysesthesia characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at 1/3 the rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table.)

Clinical Symptoms	Laryngo-pharyngeal Dysesthesia	Platinum Hypersensitivity
Dyspnoea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.

4. **Dihydropyrimidine dehydrogenase (DPD)**
Treatment with 5-fluorouracil or capecitabine products is contraindicated in patients with known complete DPD deficiency. 5-Fluorouracil must not be given to patients homozygotic for DPD. Patient with known DPD deficiency are excluded from the trial.

Routine DPD testing is not standard across all hospitals. Pre 5-fluorouracil or capecitabine treatment testing for DPD deficiency is recommended, but not mandated by the protocol. DPD deficiency testing should be performed as per local site policy.

In the event that a DPD deficiency is identified post randomisation and the patient has been randomised to a 5-fluorouracil or capecitabine containing arm, the treating investigator should remove the patient from study treatment in favour of an alternate standard of care regimen (e.g. non 5-fluorouracil/capecitabine regimen). The patient will be followed up for survival per Section 9.8 Survival Follow-up.

Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with 5-fluorouracil or capecitabine. DPD deficiency may result in severe and unexpected toxicity – stomatitis, diarrhoea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. 5-fluorouracil/ capecitabine should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhoea

5. **Possible drug interactions with capecitabine and warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (e.g., for warfarin, monitor INR weekly during capecitabine therapy and for 1 month after stopping capecitabine).

6. **Myocardial ischemia and angina** occurs rarely in patients receiving 5-fluorouracil or capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally, re-challenge with either 5-fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence

which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about 5-fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.

7. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develops – non-productive cough, dyspnoea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.

8. **Extravasation**: Oxaliplatin causes irritation if extravasated.

9. **Venous Occlusive Disease** is rare but serious complications have been reported in patients (0.02%) receiving oxaliplatin in combination with 5-fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or oesophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.

10. Oxaliplatin therapy should be interrupted if **Haemolytic Uremic Syndrome (HUS)** is suspected: haematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

6.6.1.4 Dose Modifications for Arm A: FLOT Regimen

Table 14: Dose Modifications for Arm A- FLOT

General guidelines for Docetaxel:
In patients who experience severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel may be reduced at the investigator's discretion. If the patient continues to experience these reactions at dose level -2, docetaxel treatment should be discontinued.

Dose Levels for All Toxicity

Agent	Starting Dose	Dose Level –1	Dose Level –2*
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
5-fluorouracil	2600 mg/m^2	2000 mg/m^2	1600 mg/m^2
Docetaxel	50 mg/m^2	40 mg/m^2	30 mg/m^2

* For any additional dose reductions, use 20% less than previous level or consider discontinuing this regimen.

Dose modification for Haematological Toxicities for FLOT

Prior to a Cycle (Day 1)	Toxicity		Dose Level for Subsequent Cycles		
	Grade	ANC (x10^9/L)	Oxaliplatin	5-fluorouracil	Docetaxel
• If ANC < 1.5 on Day 1 of a cycle, hold treatment. Perform FBC, maximum of 2 times. If delayed 2 weeks and on G-CSF, consider discontinuing. • If ANC is greater than or equal to 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s).	1	≥ 1.5	Maintain dose level	Maintain dose level	Maintain dose level
	2	1.0 to < 1.5	Maintain dose level	Maintain dose level	Maintain dose level
	3	0.5 to < 1.0	↓ 1 dose level	Maintain dose level	↓ 1 dose level
	4	< 0.5	↓ 1 dose level	↓ 1 dose level	↓ 1 dose level

	Grade	Platelets ($x10^9$/L)	Oxaliplatin	5-fluorouracil	Docetaxel
• If platelets < 100 on Day 1 of cycle, hold treatment. Perform weekly FBC, maximum of 2 times. • If platelets ≥100 within 2 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remain <100 after 2 weeks, discontinue treatment.	1	≥ 100	Maintain dose level	Maintain dose level	Maintain dose level
	2	50 to < 100	Maintain dose level	Maintain dose level	Maintain dose level
	3	10 to < 50	↓ 1 dose level	Maintain dose level	↓ 1 dose level
	4	< 10	↓ 2 dose levels	Maintain dose level	↓ 1 dose level

1. G-CSF primary prophylaxis can be administered at the investigators' discretion, and during the trial
2. Secondary prophylaxis with G-CSF can be used to prevent treatment delays in patients who, in a previous cycle, have experienced febrile neutropenia, Grade 4 neutropenia, or delay of scheduled treatment because of neutropenia.
3. Decrease Docetaxel and Oxaliplatin per the above dose levels if patient experiences an episode of febrile neutropenia (despite the use of GCSF), thrombocytopenia causing bleeding, or any other clinically significant haematologic dose limiting toxicity during the prior cycle of treatment. Subsequent haematologic dose limiting toxicities lead to a further dose reduction to 50% of the initial dose. If dose limiting toxicities reoccur at the 50% dose level, the clinician may remove or more of the drugs.
4. If WCC fall <2 x 10^9 / L, and especially if there is granulocytopenia, it is recommended that the patient be placed in protective isolation in the hospital and treated with appropriate measures to prevent systemic infection.

Dose modification for Neurologic Toxicities for Oxaliplatin

Peripheral Neuropathy Grade*	Dose Modification of oxaliplatin
Grade 1	Maintain dose
Grade 2 paraesthesia persisting until next cycle	Reduce dose to 65 mg/m^2
Grade 3: paraesthesia first occurrence paraesthesia persisting until next cycle	 Reduce dose to 65 mg/m^2 Discontinue oxaliplatin
Grade 4 of any duration	Discontinue oxaliplatin
Pharyngo-laryngeal (see precautions)**	Increase duration of infusion to 6 hours

** Usually, discontinuation will be permanently. Nevertheless, administration of oxaliplatin can be resumed (e.g. after complete recovery from the related symptoms) if the investigator decides that this is in the best interest of the patient and does not expect the toxicity to reoccur.*

***** Pharyngo-laryngeal dysesthesia (investigator discretion used for grading):** Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe*

Dose modification for Renal Toxicities for FLOT

Oxaliplatin	Creatinine clearance	Oxaliplatin dose
	Moderate Renal impairment CrCl* >30 ml/min	100%

	≤ 30 ml/min	Omit oxaliplatin
5-fluorouracil	Consider dose reduction in severe renal impairment only	
Docetaxel	No dose reduction necessary	

** Creatinine clearance should be calculated or measured at baseline and prior to each cycle of chemotherapy. Creatinine clearance should be calculated using the Cockcroft-Gault Formula (Appendix M). If the serum creatinine is above normal, then creatinine clearance should be measured not estimated. Dose modifications should be according to the table above.*

Dose modification for Hepatic Toxicities for FLOT

Oxaliplatin	Little information available. Probably no dose reduction necessary. Clinical decision.					
5-fluorouracil	Clinical decision. Moderate hepatic impairment; reduce dose to 33%. Severe hepatic impairment, reduce dose to 50%.					
Docetaxel	**Alkaline Phosphatase**		**AST and/or ALT**		**Serum Bilirubin**	**Dose**
	> 2.5 ULN	**AND**	> 1.5 ULN		≤ ULN	100%
	> 6 ULN	**AND/OR**	> 3.5 ULN (AST and ALT)	**AND**	> ULN	Stop Docetaxel unless strictly indicated. Clinical decision.

Mucositis and Stomatitis – for 5-fluorouracil					
Grade	**Mucositis and Stomatitis**	**1st Event Dose**	**2nd Event Dose**	**3rd Event Dose**	**4th Event Dose**
2	Painful erythema, oedema, or ulcers but can eat	Delay* then 100%	Delay* then 75%	Delay* then 50%	Omit 5-fluorouracil
3 or 4	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Delay* then 50 %	Omit 5-fluorouracil		
**Stop treatment immediately and delay until resolved to grade 0-1*					

Dose adjustments in case of other toxicities for FLOT

Adverse reactions	**Recommended dose modification**
Grade ≥ 3 Non-haematological toxicity*	
- First occurrence	Decrease dose of all drug(s) to 75% **
- Second occurrence	Decrease dose of all drug(s) to 50% **
- Further occurrence	Discontinue relevant drug(s)**

*** Relevant drug(s) refers to the chemotherapeutic agent most likely responsible for the observed toxicity.*

Cystoid macular Oedema:

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. If CMO is diagnosed, docetaxel treatment should be discontinued, and appropriate treatment initiated.

Dihydropyrimidine dehydrogenase (DPD)
Treatment with 5-fluorouracil products is contraindicated in patients with known complete DPD deficiency. 5-Fluorouracil must not be given to patients homozygotic for DPD. Patient with known DPD deficiency are excluded from the trial.

Routine DPD testing is not standard across all hospitals. Pre 5-fluorouracil or capecitabine treatment testing for DPD deficiency is recommended, but not mandated by the protocol. DPD deficiency testing should be performed as per local site policy.

In the event that a DPD deficiency is identified post randomisation and the patient has been randomised to a 5-fluorouracil or capecitabine containing arm, the treating investigator should remove the patient from study treatment in favour of an alternate standard of care regimen (e.g. non 5-fluorouracil/capecitabine regimen). The patient will be followed up for survival per Section 9.8 Survival Follow-up.

Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with 5-fluorouracil or capecitabine. DPD deficiency may result in severe and unexpected toxicity – stomatitis, diarrhoea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. 5-fluorouracil/ capecitabine should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhoea

6.6.2 Dose Modifications for Arm B – CROSS Regimen

Chemotherapeutic toxicity

Hematologic Related Toxicity
If on day 1, 8, 15 or 22 the neutrophils are < 1.0 and/or platelets < 50: delay chemotherapy by 1 week until recovery above these values. If on day 29 the neutrophils are < 1.0 and/or platelets < 50: withhold chemotherapy.
In case of febrile neutropenia (neutrophils< 0.5/L and fever > 38.5°C) or in case of severe bleeding or requiring ≥ 2 platelet transfusions further chemotherapy will be withheld.

Non-hematologic Toxicity
These effects will be graded according to CTCAE recommendations for grading of acute and sub acute toxicity.

Hypersensitivity Reactions
Hypersensitivity reactions will be classified as mild, moderate or severe. Definitions and management guidelines are outlined below:

Table 15: CROSS: Hypersensitivity reactions after chemotherapy: classification and management

Classification of reactions	Management of reactions
One or more mild symptoms: ▪ Mild flushing ▪ Rash ▪ Pruritus	Complete chemotherapy infusion with supervision at bedside. No treatment required
One or more moderate symptoms: ▪ Moderate rash ▪ Flushing ▪ Mild dyspnoea ▪ Chest discomfort ▪ Mild hypotension	Stop chemotherapy infusion, venous infusion of antihistamine (chlorphenamine 10 mg IV or equivalent and dexamethasone* 10 mg IV* or equivalent), → after recovery of symptoms resume paclitaxel infusion at a rate of 25% rate for at least 5 minutes, 50% rate for at least 5 minutes, 75% rate for at least 5 minutes and then resume remainder of infusion at full rate if no reaction[36]
One or more severe symptoms: ▪ Respiratory distress requiring treatment ▪ Generalized urticaria ▪ Angioedema ▪ Hypotension requiring therapy	Stop chemotherapy infusion; give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated, report as an adverse event, the patient will go off protocol therapy

**Venous infusion of dexamethasone 10mg IV can be replaced with hydrocortisone 100mg IV, according to hospital institutional policy.*

Other toxic reactions and the prescribed management of these reactions are outlined in the following table:

Table 16: CROSS Toxic Reactions and Prescribed management

Reaction	Management of reactions
Renal Impairment: CrCl **> 30 ml/min** CrCl ≤ **30 ml/min**	 No dose modification required Omit Carboplatin
Hepatic Impairment * Mild Moderate Severe	 Paclitaxel 25% reduction Paclitaxel 50% reduction Discontinue Paclitaxel
Gastrointestinal: Mucositis with oral ulcers or protracted vomiting despite antiemetic premedication	Delay chemotherapy one week
Neurologic: CTCAE grade ≤ 2 CTCAE grade > 2	 Continue therapy Stop chemotherapy
Cardiac: Asymptomatic bradycardia or isolated asymptomatic ventricular extrasystoles First degree AV block Symptomatic arrhythmia or AV block (except 1st degree) or other heart blocks	 Continue therapy under continuous cardiac monitoring Continue therapy under continuous cardiac monitoring Stop chemotherapy, manage arrhythmia according to standard practice. Consider continuation of treatment following discussion with CI once episode resolved and patient has undergone appropriate management. Patient may need to go off protocol (CI decision).
Other Major Organ Toxicity: CTCAE grade > 2 (With the exception of oesophagitis)	 Stop therapy, patient goes off protocol treatment.

**Refer to Appendix O: Classification for Hepatic Dysfunction*

6.6.3 Radiation toxicity

Radiotherapy, especially concurrent with chemotherapy can lead to acute oesophagitis. In some cases, medical support and/or a feeding tube will be necessary.
In the event of grade 4 radiation induced oesophagitis both chemotherapy and radiotherapy will be withheld until the oesophagitis recovered to grade 3.

Radiotherapy, especially concurrent with Taxanes, can lead to acute radiation pneumonitis. For many years, 3 Dimensional Conformal Radiation Therapy (3D CRT) has been the standard of care radiotherapy technique. However, increasingly Intensity Modulated Radiation Therapy (IMRT) is being utilised to reduce the radiation dose to surrounding organs while maintaining tumour control.[40,41] However, caution must be applied as even low doses of radiation, such as those received by the lungs using IMRT may result in a higher rate of pulmonary complications, including radiation pneumonitis.[42,43,44] With this mind, conservative guidelines have been prepared for sites using IMRT in this trial. 4DCT planning and treatment should be used for all patients treated with IMRT. A number of key dosimetric variables will be captured in order to record the dose received by the lungs. Other acute complications of the radiation therapy are erythema, cough, nausea, fatigue and weight loss.

7. Patient Selection Criteria

Countries with Group Specific Appendices with sections relating to the inclusion and exclusion criteria, should refer to this document when reviewing patient eligibility.

7.1 Inclusion Criteria

1. Histologically verified adenocarcinoma of the oesophagus, or oesophago-gastric junction based on OGD.
2. CT- ^{18}FDG-PET performed in all patients for disease staging
3. EUS in all patients unless luminal obstruction precludes sensitivity of the test.
4. Staging laparoscopy will be performed at the investigator's discretion for locally advanced AEG II and AEG III tumours.
5. Pre-treatment stage cT2-3, N0-3, M0.
6. Maximum tumour length should be no more than 8cm (equal to 8 cm is acceptable).
7. Male/female patients aged ≥18 years.
8. ECOG Performance Status 0, 1 or 2 (Appendix D).
9. ASA Grading I-II (Appendix D).
10. Adequate cardiac function. For all patients, an ejection fraction of > 50% is required. If patients have a known history of significant cardiac disease (e.g. known ischemic disease, cardiomyopathy) an ejection fraction > 50% and cardiac clearance by a consultant cardiologist for major surgery and cancer therapies is required.
11. Adequate respiratory function. Patients should have pulmonary function tests completed with a minimum FEV1≥1.5L. CPEX acceptable.
12. Adequate bone marrow function: absolute neutrophil count (ANC) >1.5x10^9/l; white blood cell count > 3x10^9/l; platelets > 100x10^9/l; haemoglobin (Hb) > 9g/dl (can be post-transfusion).
13. Adequate renal function: glomerular filtration rate > 60ml/minute calculated using the Cockcroft-Gault Formula (Appendix M).
14. Adequate liver function: serum bilirubin ≤ ULN; AST <2.5x ULN and ALP <3x ULN (ULN as per institutional standard).
15. Written informed consent must be obtained from the patient before any study-specific procedures are performed.
16. Women of child-bearing potential and male subjects must agree to use an effective barrier method of contraception for up to 6 months following discontinuation of therapy. Effective barrier method of contraception is defined as any medically recommended (or combination of methods) as per standard of care.
17. Women of child bearing potential must have pregnancy excluded by urine or serum beta-HCG testing within 7 calendar days prior to registration.

7.2 Exclusion Criteria

1. Tumours of squamous histology.
2. Patients with advanced inoperable or metastatic oesophageal, junctional or gastric adenocarcinoma.
3. Disease length (total length of tumour plus node) greater than 10 cm (up to 10 cm will be allowed) -*measured by any modality or, if appropriate, combination of modalities-,* unless in the opinion of the investigator in discussion with national RT lead, it is felt that OAR constraints are likely to be achievable.
4. Any prior chemotherapy for gastrointestinal cancer.
5. Prior abdominal, thoracic, chest wall or breast radiotherapy.

6. Patients who are unfit for surgery or cancer treatments based on cardiac disease.
7. Patients with acute systemic infections.
8. Patients who are receiving treatment with sorivudine or its chemical related analogues, such as brivudine which is contraindicated with capecitabine and 5-fluorouracil administration.
9. Clinical COPD with significant obstructive airways disease classified by FEV1 < 1.5 L or PaO_2 less than 9kPa on room air.
10. Known peripheral neuropathy >Grade 1 (absence of deep tendon reflexes as the sole neurological abnormality does not render the patient ineligible).
11. Known positive tests for human immunodeficiency virus (HIV) infection, acute or chronic active hepatitis B infection.
12. Any other malignancies within the last 5 years (other than curatively treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix).
13. Participation in other clinical trials of investigational or marketed agents for the treatment of oesophageal cancer or other diseases within 30 days prior to registration. UK sites please refer to Group Specific Appendix.
14. Women who are pregnant or breastfeeding.
15. Psychiatric illness/social situations that would limit compliance with study requirements.
16. Known Dihydropyrimidine dehydrogenase (DPD) deficiency

For sites in UK, France, Denmark, Sweden and Netherlands: for inclusion and exclusion criteria, please refer to your (applicable) GSA/CSA.

8. Patient Enrolment Procedure

8.1 PATIENT ENROLMENT

Patients will be considered as enrolled in the trial after informed consent and registration has occurred. Potential patients will be screened and enrolled in the trial on the basis of the inclusion/exclusion criteria specified in the protocol. At registration, each patient will be assigned a trial number, which will be used to identify the patient. Before patients may be enrolled into the trial, the Sponsor must receive proof that all required regulatory approval (both local and, if relevant, national) has been obtained for the site. Before registration, each potential patient must be given a patient information sheet and informed consent must be obtained according to the requirements of International Conference on Harmonisation of Good Clinical Practice (ICH GCP). The registration and baseline assessment forms must also be completed. Only patient fulfilling all inclusion criteria, and without any exclusion criteria should be entered for registration. Any queries about eligibility or registration should be addressed directly to the Chief Investigator via Cancer Trials Ireland. Please note for trial purposes, “registration” will be used throughout for consistency instead of “randomisation” although the term is interchangeable.

The investigator will retain a list of all patients screened as well as enrolled in the trial and a screening log will be retained in the investigator's trial file and to be sent to the Sponsor periodically for review. Screening log to be completed for patients with newly presenting adenocarcinoma of the oesophagus or OGJ who appear to be candidates to fulfil clinical (radiological, endoscopic, fitness) eligibility criteria for treatment with curative intent including major thoracic surgery. Please refer to the country-specific screening log for further guidance on candidate suitability, if applicable. Full written informed consent must be obtained from a patient before they can be registered on the trial. The investigator (or designated trial personnel) should check that the eligibility criteria are met and complete the patient registration form. If the patient is eligible for inclusion and patient consent is obtained, the site should send the patient registration form to the Cancer Trials Ireland Office:

Fax Number: +353 (0)1 6697869
Telephone Number: +353 (0)1 6677211

E-mail address: patientregistrations@cancertrials.ie

The patient registration form will be checked and once all information has been verified Cancer Trials Ireland will email confirmation of registration back to the site assigning a unique patient number to the patient together with treatment arm allocation. Please note that when registering a patient for the first time, a copy of the complete Delegation of Duties Log must accompany the Patient Registration Form. Incomplete or illegible forms will not be processed and will be sent back for completion or review. Your country may also have a specific work instruction for this procedure, please make sure to follow it to avoid delays when submitting a registration form.

Treatment should commence within 21 calendar days following the day of registration ('day 0') (+3 days window is allowed due to holidays or clinic schedule).

9. Study Assessments and Procedures

A signed, written informed consent form approved by the Ethics Committee must be obtained from the patient prior to any trial-specific assessments and procedures being carried out. The trial assessments schedules and visit windows are summarised in Tables 17 - 24.

Table 17: Study Assessments and Procedures: Screening - Registration

	Screening Visit[a]	Registration	Post Registration/ Pre- Treatment Visit (within 15 days prior to onset of treatment)*
Visit to specialist Unit	X		X
Medical History (including smoking and alcohol history and evidence of dysphagia)	X		
Physical examination	X		X
ECOG Performance Status	X		X
ASA Grading	X		
Informed Consent	X		
EORTC C30 QLQ (Including EORTC QOL – OES 18) Questionnaire [b]	X		
Clinical Lab Tests [c]	X		X
CT-PET thorax, abdomen and neck[d]	X		
EUS[d]	X		
OGD and Biopsy evidence of adenocarcinoma[d]	X		
Laparoscopy (as clinically indicated) [d]	X		
Upper GI MDT discussion to confirm staging[j]	X		
Pre-treatment Staging (TNM stage & overall stage)	X		
Weight	X		X
Height	X		
Vital Signs			X
Eligibility Criteria Assessment		X	
Electrocardiogram [k]	X		
MUGA/ECHO [k][e]	X		
Pulmonary function testing (CPEX acceptable) [k]	X		
Urine or serum beta HCG testing [f]	X[f]		X[f]
Hearing assessment [g]	X		
Review Concurrent Medications	X		X
Blood samples and biopsies for translational research/biobank (SJH patients only) [h]	X[i]		
Registration		X	
Simulation for radiotherapy (arm B only)			X (Date for simulation to be organised post Rad. Onc. Visit)

*can happen on C1D1.

(a) The screening procedures must be completed within 28 calendar days before registration, unless specified in section 9.2 of the protocol.

(b) If performing the EORTC C30 QLQ (Including EORTC QOL – OES 18) Questionnaire is not part of the institutional standard practice for these patients then the Patient Information Leaflet and Consent form must be signed before the patient completes the questionnaire. If this questionnaire is part of the institutional standard practice for these patients, then the Patient Information Leaflet and Consent form does not need to be signed before the patient completes the questionnaire.

(c) Full blood count, Renal Profile (including creatinine clearance, BUN/ Urea), Liver profile, Bone Profile. Coagulation screen (INR and/or PT (Prothrombin time) assessments) to be performed for all patients at screening, and only if clinically indicated at post-registration visit.
(d) These procedures do not need to be repeated if completed within 42 calendar days prior to the day of registration ('day 0'). However, if the procedure was not completed within 6 weeks prior to registration and it is not possible to repeat the procedure, the last staging investigation which may include CT, PET/CT, EUS or laparoscopy, should normally be performed within 28 calendar days prior to the day of registration ('day 0'). For EUS, these should be performed unless luminal occlusion precludes sensitivity of the test.
(e) Patients must have adequate cardiac function to participate in this trial. For patients with a known significant cardiac history (e.g. known ischemic heart disease, cardiomyopathy) an ejection fraction > 50% and cardiac clearance by a consultant cardiologist for major surgery and cancer therapies is required.
(f) Female patients of childbearing potential should have pregnancy excluded by urine or serum beta-HCG testing within 7 calendar days prior to registration and 7 calendar days prior to treatment. The screening pregnancy test does not need to be repeated prior to treatment if the test is within 7 calendar days to treatment.
(g) Assessment of hearing should be performed during medical history evaluation and audiometric testing to be performed if clinically indicated. Please note that cisplatin is contraindicated in patients with hearing loss.
(h) Prior to registration, patients will be invited to consent to having some of their tissue and blood taken for the SJH upper GI biobank project (using the SJH biobanking consent form). These samples will generally be taken at the same time as biopsied for histological diagnosis. At the time of screening, the patient will be invited to consent to use their sample from the biobank for the research proposed in this protocol. Additional blood samples or tissue can be obtained after registration/prior to treatment, if required.
(i) If not collected at the screening visit, sample to be collected prior to Cycle 1 Day 1 (C1D1) (SJH patients only)
(j) For UK sites, please refer to Group Specific Appendix for further guidance on these timelines.
(k) This procedure does not need to be repeated if done within 42 calendar days prior registration

Table 18: Study Assessments and Procedures for Arm A: MAGIC (neoadjuvant treatment pre-surgery)

	MAGIC ECF/ECX or EOF/EOX Regimen [a]			End of Neoadjuvant Treatment Visit [g]	Pre-surgery visit
STUDY DAY	1 (Cycle 1)	22(Cycle2)	43(Cycle 3)	30 – 42 days post last dose	28 – 56 days post last dose
Epirubicin 50mg/m^2	X	X	X		
Cisplatin 60mg/m^2 <u>or</u> Oxaliplatin 130mg/m^2	X	X	X		
5-FU[b] 200 mg/m^2/day continuous infusion <u>or</u> Capecitabine 625mg/m ^{2} twice daily orally	X	X	X		
Capecitabine compliance check		X	X	X	
Oncology Dr Assessment [h]	X	X	X		
Clinical History and Physical examination [c] [h]	X	X	X		X (including evidence of dysphagia)
ECOG Performance Status[h]	X	X	X		X
ASA Grading					X
Concurrent Meds	X	X	X	X	
Adverse Event evaluation	X	X	X	X	X
Disease Progression	Monitored throughout trial				
Clinical Lab Tests [d]	X	X	X		X
Coagulation screen (INR and/or prothrombin time (PT) assessments) [d]	If clinically indicated				X
Weight	X	X	X		X
Height	X				
Vital Signs	X	X	X		
Restaging PET-CT or CT [e]					X
Restaging OGD [e]					X
Restaging Laparoscopy as indicated [f]					X
Upper GI MDT discussion					X (post-restaging)
EORTC C30 QLQ (Including EORTC QOL – OES 18)					X

All of the post registration pre-treatment visit assessment results (e.g., blood tests) do not need to be repeated if performed within 7 calendar days of C1D1.

(a) Treatment consists of 3 cycles of chemotherapy pre-surgery and 3 cycles post-surgery. Each cycle lasts 3 weeks/ 21 days

(b) 5-fluorouracil to commence on day 1 of each cycle but continues as a continuous IV infusion via a pump till day 21 until commencement of the next cycle. Pump changes occur at day 1, day 8 and day 15 of each cycle. <u>OR</u> they may receive capecitabine 625mg/m ^{2} orally twice daily as an alternative to the 5-fluorouracil pump. This is at the discretion of the investigator.

(c) Physical examination to include a hearing assessment, if clinically indicated.

(d) Full blood count, Renal Profile (including creatinine clearance, BUN/Urea), Liver profile, Bone Profile. These should be done at the start of each cycle or more frequently as clinical condition requires. They should also be done at the pre-surgery visit. If blood test results are available as per the post registration visit, these do not need to be repeated if completed within 7 calendar days from C1D1.

Coagulation screen (INR and/or PT assessments) to be performed if clinically indicated during treatment, and to be performed at the pre-surgery visit.

(e) Restaging PET-CT or CT and OGD should occur within 4-8 weeks of finishing treatment. Countries where local standard of care mandates this to happen immediately after neoadjuvant treatment, is also acceptable.

(f) Restaging laparoscopy will be carried as per the investigator's discretion. This will be performed if indicated when the patient is admitted to hospital for surgery.

(g) End of neoadjuvant treatment visit performed to review adverse events, capecitabine compliance check. Please see Appendix N if further guidance on adverse event collection is needed. In countries where per standard of care, this visit and the pre-surgery visit fall within the same timeframe, these visits can be combined.

(h) The following assessments should be performed on, or within 5 calendar days prior to, day 1 of each cycle of treatment. All other assessments should be completed within 3 calendar days prior to day 1 of each cycle of treatment.

Table 19: Study Assessments and Procedures for Arm A: FLOT (neoadjuvant treatment pre-surgery)

	FLOT Regimen [a, b]				End of Neoadjuvant Treatment Visit [g]	Pre-surgery visit
STUDY DAY	Day 1 Cycle 1	Day 15 Cycle 2	Day 29 Cycle 3	Day 43 (Cycle 4)	30 – 42 days post last dose	28-56 days post last dose
Docetaxel 50 mg/m²	X	X	X	X		
Oxaliplatin 85 mg/m²	X	X	X	X		
Leucovorin 200 mg/m²	X	X	X	X		
5-Fluorouracil 2600 mg/m²	X	X	X	X		
Oncology Dr Assessment [h]	X	X	X	X		
Clinical History and Physical examination [c] [h]	X	X	X	X		X (including evidence of dysphagia)
ECOG Performance Status[h]	X	X	X	X		X
ASA Grading						X
Concurrent Meds	X	X	X	X	X	
Adverse Event evaluation	X	X	X	X	X	X
Disease Progression	Monitored throughout trial					
Clinical Lab Tests [d]	X	X	X	X		X
Coagulation screen (INR and/or PT assessments) [d]	If clinically indicated					X
Weight	X	X	X	X		X
Height	X					
Vital Signs	X	X	X	X		
Restaging PET-CT or CT [e]						X
Restaging OGD [e]						X
Restaging Laparoscopy as indicated [f]						X
Upper GI MDT discussion						X (post-restaging)
EORTC C30 QLQ (Including EORTC QOL – OES 18)						X

The post registration pre-treatment visit assessment results (e.g., blood tests) do not need to be repeated if performed within 7 calendar days of C1D1.

(a) The FLOT regimen consists of Docetaxel 50 mg/m² IV day 1, Oxaliplatin 85 mg/m² IV day 1, Leucovorin 200 mg/m² IV day 1, and 5-fluorouracil 2600 mg/m² IV 24hr infusion day 1

(b) Treatment consists of 4 cycles of chemotherapy pre-surgery and 4 cycles post-surgery. Each cycle lasts 2 weeks/ 14 days

(c) Hearing assessment are not required for FLOT patients.

(d) Full blood count, Renal Profile (including creatinine clearance, BUN/Urea), Liver profile and Bone Profile. These should be done at the start of each cycle or more frequently as clinical condition requires. They should be done at the pre surgery visit. If blood test results are available as per the post registration visit, these do not need to be repeated if completed within 7 calendar days from C1D1.
Coagulation screen (INR and/or PT assessments) to be performed if clinically indicated during treatment, and to performed at the pre-surgery visit.

(e) Restaging PET-CT or CT and OGD should occur within 4-8 weeks of finishing treatment. Countries where local standard of care mandates this to happen immediately after neoadjuvant treatment, is also acceptable.

(f) Restaging laparoscopy will be carried as per the investigator's discretion. This will be performed if indicated when the patient is admitted to hospital for surgery.

(g) End of neoadjuvant treatment visit performed to review adverse events. Please see appendix N if further guidance on adverse event collection is needed. In countries where per standard of care, this visit and the pre-surgery visit fall within the same timeframe, these visits can be combined.

(h) The following assessments should be performed on, or within 5 calendar days prior to, day 1 of each cycle of treatment. All other assessments should be completed within 3 calendar days prior to day 1 of each cycle of treatment.

Table 20: Study Assessments and Procedures for Arm B

	The CROSS Multi-modality Regimen [a]					Post CROSS Follow-up Visit[f]	Pre-surgery Visit
STUDY DAY	1	8	15	22	29	30 – 42 days post last dose	28-56 days post last dose
Radiotherapy (41.4 Gy/23 fractions)[a]	X	X	X	X	X		
Paclitaxel [a] 50mg/ m^2	X	X	X	X	X		
Carboplatin [a] AUC=2	X	X	X	X	X		
Oncology/radiation oncology Dr Assessment[g,]	X	X	X	X	X		
Clinical History and Physical examination [g,h]	X	X	X	X	X		X (including evidence of dysphagia)
ECOG Performance Status[g, h]	X	X	X	X	X		X
ASA Grading							X
Concurrent Meds	X	X	X	X	X	X	
Adverse event evaluation	X	X	X	X	X	X	X
Disease Progression	Monitored throughout trial						
Clinical Lab Tests[b]	X	X	X	X	X		X
Coagulation screen (INR and/or PT assessments)[b]	If clinically indicated						X
Weight	X	X	X	X	X		X
Height	X						
Vital Signs [c]	X	X	X	X	X		
Restaging PET-CT or CT [d]							X
Restaging OGD[d]							X
Restaging Laparoscopy [e]							X
Upper GI MDT discussion							X (post-restaging)
EORTC C30 QLQ (Including EORTC QOL – OES 18)							X

The post registration pre-treatment visit assessment results (e.g., blood tests) do not need to be repeated if performed within 7 calendar days of day 1.

(a) Treatment consists of a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive 4 and a half weeks of radiation therapy (41.4 Gy/23 fractions) and 5 cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. The radiation will generally commence on the 1st day of treatment and will run for 5 weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29.

(b) Full blood count, Renal Profile (including creatinine clearance, BUN/Urea), Liver profile, Bone Profile. These should be done within 3 calendar days prior to day 1 of each cycle of treatment or more frequently as clinical condition requires. They should be done at pre-surgery visit. If blood test results are available as per the post registration visit, these do not need to be repeated if completed within 7 calendar days from day 1. Coagulation screen (INR and/or PT assessments) to be performed if clinically indicated during treatment, and to be performed at the pre-surgery visit.

(c) It is possible that some patients may experience asymptomatic bradycardia during the Paclitaxel infusion. In addition, hypersensitivity reactions are possible and generally occur within the first few minutes of initiating the infusion. For these reasons, it is recommended that there is constant supervision and that the vital signs are monitored every 15 minutes during Paclitaxel administration. Thereafter patients may be observed, and heart rate and blood pressure checked if necessary, according to clinical symptoms.

(d) Restaging PET-CT or CT and OGD should occur within 4-8 weeks of finishing treatment. Countries where local standard of care mandates this to happen immediately after neoadjuvant treatment, is also acceptable.
(e) Restaging laparoscopy will be carried as per the investigator's indication. This will be performed if indicated when the patient is admitted to hospital for surgery.
(f) Post CROSS Follow-up Visit should be performed by medical/radiation oncology either by hospital visit or phone conversation. Adverse events must be collected for a period of 30 days after the last dose of chemo-radiation treatment (day 31). See Appendix N for further guidance. In countries where per standard of care, this visit and the pre-surgery visit fall within the same timeframe, these visits can be combined.
(g) The following assessments should be performed on, or within 5 calendar days prior to, day 1 of each cycle of treatment all other assessments should be completed within 3 calendar days prior to day 1 of each cycle of treatment (exception for C1D1 where post registration assessments do not need to be repeated if performed within 7 calendar days prior to D1 visit).
(h) The following assessments should be performed on, or within 5 calendar days prior to, day 1 of each cycle of treatment. All other assessments should be completed within 3 calendar days prior to day 1 of each cycle of treatment.

Table 21: Study Assessments and Procedures Post-Surgery

	Arm A [(b)] Arm B	Arm A [(b,f)] Arm B	Arm A [(b,f)] Arm B	Arm A [(g)] Arm B	Arm A [(h)] Arm B	Arm A [(h)] Arm B
STUDY DAY	2 weeks-1 month post-discharge [(a)]	3 months post-surgery	6 months post-surgery	9 months post-surgery	1/1.5/2/2.5/ 3/3.5/4/4.5/5 years post-surgery [(e)]	every 6 months thereafter[(e)]
Visit to Trial Centre	X	X	X	X	X	
Clinical History and Physical examination	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	
Assessment of operative and treatment related toxicity	X	X	X	X	X	
EORTC C30 QLQ Questionnaire (Including EORTC QOL – OES 18) [(c)]		X	X		X	
Weight	X	X	X	X	X	
Clinical Lab Tests	X[(d)]	X[(d)]	X[(d)]	X[(d)]	X[(d)]	
Survival Follow-up						X
Disease Progression	Monitored throughout trial					

(a) 1st visit post-operatively may be within 2-4 weeks post-discharge from hospital post-surgery. 1st visit is often dependent upon the patients' clinical condition at discharge. Subsequent visits may be alternatively scheduled as patient condition dictates for both Arm A and B patients.
(b) For Arm A patients, follow-up visits post-surgery will occur concomitantly with visits for adjuvant treatment.
(c) Quality of life (EORTC QLQ C30 and EORTC QLQ-OES 18)) will be performed during follow up at 3 months, 6 months, 1 year, 2 years and 3 years after completion of trial treatment (Appendix E). Year 2 and 3 assessments are not applicable if they are due post End of Trial
(d) Clinical laboratory investigations will only be carried out as clinically indicated, at the investigator's discretion
(e) Patients will be followed-up until death or the end of the trial, whichever occurs earlier. The end of trial is defined as when the last patient has completed 18 months follow-up, i.e. 18 months post randomisation.:
- Follow-up visits will be scheduled every 6 months after completion of year 1 for maximum of 5 years or until disease progression, or end of trial, whichever occurs earlier.
- Post disease progression or 5 years standard follow-up, patients will be followed up for survival every 6 months until death or until the end of the trial, whichever occurs earlier.

(f) A +/- 2 week visit window is allowed to schedule the following visits: 3 and 6 month post-surgery visit

(g) A +/- 4 week visit window is allowed to schedule the following visit: 9 month post-surgery visit
(h) A +/- 6 week window is allowed to schedule the following visits: 1 year post-registration / 1 year post-surgery; 18 months post-surgery and every 6 months during standard and survival follow-up.

Table 22: Disease Assessments (Both treatment arms)

Timepoint	1 year post-registration (a, b,c)	2 year post-registration* (a,b,c)	3 year post-registration* (a,b,c)
Radiological tests (CT or CT/PET as clinically indicated)	X	X	X
OGD	X	X	X
Disease Progression	Monitored throughout trial		

(a) CT or CT/PET and OGD should be carried out at 1, 2 and 3 years post registration (and as clinically indicated thereafter)*. This is to ensure consistent documentation of local (including anastomotic) recurrence as well as systemic relapse. Please refer to your Group-specific appendix / Country-specific appendix (GSA/CSA)
(b) for further guidance on how to proceed in your country if the described is not in line with your local standard of care.
(c) A +/- 6 week window is allowed for each assessment
(d) Assessments can be incorporated into one of the standard post-surgery follow-up visits.

** Year 2 and 3 assessments are not applicable if they are due post End of Trial.*

Table 23: Study Assessments and Procedures for Arm A: MAGIC (adjuvant treatment post-surgery)

	MAGIC ECF/ECX or EOF/EOX Regimen (a)			Post Treatment(e)
Cycle	(Cycle 4)	(Cycle 5)	(Cycle 6)	30 - 44 days post last treatment
Visit to oncology unit for 3 cycles adjuvant chemotherapy (b)	X	X	X	
Epirubicin 50mg/m2	X	X	X	
Cisplatin 60mg/m2	X	X	X	
5-FU (c) 200 mg/m2/day continuous infusion **Or** Capecitabine 625mg/m ^{2} twice daily orally	X	X	X	
Capecitabine compliance check		X	X	X
Oncology Assessment	X	X	X	
Clinical History and Physical examination	X	X	X	X
ECOG Performance Status	X	X	X	X
Concurrent Meds	X	X	X	X
Adverse event evaluation	X	X	X	X
Disease Progression	Monitored throughout trial			
Clinical Lab Tests (d)	X	X	X	X
Coagulation screen (INR and/or PT assessments) (d)	If clinically indicated			
Weight	X	X	X	X
Vital Signs	X	X	X	
Visit to Trial Centre (e)				X

(a) Treatment consists of 3 cycles of chemotherapy pre-surgery and 3 cycles post-surgery. Each cycle lasts 3 weeks/ 21 days

(b) Consideration of postoperative chemotherapy should be considered after the 1st visit back to the surgery trial doctor. Adjuvant chemotherapy should be initiated 6-12 weeks post-surgery or at the investigator's discretion.
(c) 5-fluorouracil to commence on day 1 of each cycle but continues as a continuous IV infusion via a pump till day 21 until commencement of the next cycle. Pump changes occur at day 1, day 8 and day 15 of each cycle. **OR** they may receive capecitabine 625mg/m ^{2} orally twice daily as an alternative to the 5-fluorouracil pump. This is at the discretion of the investigator.
(d) Full blood count, Renal Profile (including creatinine clearance), Liver profile, Bone Profile. These should be done at the start of each cycle and post treatment or more frequently as clinical condition requires. Coagulation screen (INR and/or PT assessments) only if clinically indicated.
(e) Following oncology treatment and initial follow up (30-44 calendar days post last day of treatment), patients will be linked back to the trial centre and will continue to be followed-up by the trial team as per Tables 21 and 22. For patients who are on Capecitabine the post treatment follow-up visit will take place 30 (+3) calendar days post the last capecitabine dose.

Table 24: Study Assessments and Procedures for Arm A: FLOT (adjuvant treatment post-surgery)

	FLOT[a,b]				Post Treatment Visit[e]
Cycle	Cycle 5	Cycle 6	Cycle 7	Cycle 8	30 - 44 days post last treatment
Visit to oncology unit for adjuvant chemotherapy [c]	X	X	X	X	
Docetaxel 50 mg/m²	X	X	X	X	
Oxaliplatin 85 mg/m²	X	X	X	X	
Leucovorin 200 mg/m²	X	X	X	X	
5-Fluorouracil 2600 mg/m²	X	X	X	X	
Oncology Assessment	X	X	X	X	
Clinical History and Physical examination	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X
Concurrent Meds	X	X	X	X	X
Adverse event evaluation	X	X	X	X	X
Disease Progression	Monitored throughout trial				
Clinical Lab Tests [d]	X	X	X	X	X
Coagulation screen (INR and/or PT assessments) [d]	If clinically indicated				
Weight	X	X	X	X	X
Vital Signs	X	X	X	X	
Visit to Trial Centre [e]					X

(a) The FLOT regimen consists of, Docetaxel 50 mg/m² IV day 1, Oxaliplatin 85 mg/m² IV day 1 Leucovorin 200 mg/m² IV day 1 and 5-fluorouracil 2600 mg/m² IV 24 hr infusion day 1.
(b) Treatment consists of 4 cycles of chemotherapy pre-surgery and 4 cycles post-surgery. Each cycle lasts 2 weeks/14 days
(c) Consideration of postoperative chemotherapy should be considered after the 1st visit back to the surgery trial doctor. Adjuvant chemotherapy should be initiated 6-12 weeks post-surgery or at the investigator's discretion.
(d) Full blood count, Renal Profile (including creatinine clearance), Liver profile and Bone Profile. These should be done at the start of each cycle and post treatment or more frequently as clinical condition requires.
Coagulation screen (INR and/or PT assessments) only if clinically indicated.
Following oncology treatment and initial follow up (30-44 calendar days post last day of treatment), patients will be linked back to the trial centre and will continue to be followed-up by the trial team as per Table 21.

9.1 Study Procedures

Patients referred with oesophageal cancer symptoms will attend an outpatient appointment service for assessment of their disease and will complete diagnostic tests which are standard procedures to confirm and stage of their oesophageal cancer. These procedures are completed as part of the initial visit and to verify the patient's eligibility to participate in the trial.

Once staging procedures are completed, patients are discussed at a Gastro-Intestinal Multi-Disciplinary Meeting (MDT), to evaluate suitability for trial participation. If the patients are not suitable for trial participation the reason should be documented in the screening log.
Suitable patients may then be approached for consideration for inclusion to the clinical trial and will be provided with a copy of the trial approved informed consent form to decide if they are willing to participate to this trial. **The informed consent must be signed before any trial procedure is completed at the screening visit.**

9.2 Screening Visit Assessments:

The following assessments and investigations must be performed within 28 calendar days prior registration, unless otherwise specified below:

1. Obtain written Informed Consent.
2. Clinical history and physical examination, including ECOG performance status, ASA grading (Appendix D), weight and hearing assessment.
3. CT –PET scan of the thorax, abdomen and neck will be performed in all patients. **This procedure does not need to be repeated if completed within 42 calendar days prior to registration. However, if this is not possible, the last staging investigation which may include CT, PET/CT, EUS or laparoscopy, should normally be performed within 28 calendar days of registration.** ***Please refer to Table 17 letter (d), for guidance on tests older than 42 calendar days and if not feasible to repeat.***
4. Endoscopic Ultrasound* ***This procedure does not need to be repeated if done 42 calendar days prior to registration. Please refer to Table 17 letter (d), for guidance on tests older than 42 calendar days and if not feasible to repeat.***
   *Denmark: Please refer to group specific appendix
5. OGD will be performed in all patients to confirm disease diagnosis and staging. ***This procedure does not need to be repeated if done within 42 calendar days prior to registration. Please refer to Table 17 letter (d), for guidance on tests older than 42 calendar days and if not feasible to repeat.***
6. Staging laparoscopy will be performed for locally advanced AEG II and AEG III tumours per institutional practice. Nodes may be biopsied at this assessment, and peritoneal lavage will be performed for cytology. ***This procedure does not need to be repeated if done within 42 calendar days prior registration. Please refer to Table 17 letter (d), for guidance on tests older than 42 days and if not feasible to repeat.***
7. Pulmonary Function Tests. ***This procedure does not need to be repeated if done within 42 calendar days prior registration.***
8. Electrocardiogram (ECG). ***This procedure does not need to be repeated if done within 42 calendar days prior registration***
9. Full blood count (FBC): haemoglobin, white cell count, neutrophils and platelets.
10. Serum biochemistry, Renal, Liver and Bone profile: sodium, potassium, creatinine, blood urea nitrogen (BUN)/Urea, calcium, magnesium, chloride, bicarbonate (if possible), phosphate, lactate dehydrogenase (LDH), total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and serum albumin.

11. Creatinine clearance should be calculated using the using the Cockcroft-Gault Formula (Appendix M). If the calculated creatinine clearance is below 60ml/min or serum creatinine is above the local upper limit of normal, a formal assessment of glomerular filtration rate (GFR) should be performed.
12. Coagulation blood tests: INR and/or PT for all patients
13. Blood sample and collection of surplus diagnostic paraffin embedded tumour tissue for exploratory analyses (For SJH patients only, see section 5)
14. Quality of life (EORTC QLQ C30 (Including EORTC QLQ-OES 18)) (see Appendix E).
15. Assessment of left ventricular ejection fraction (LVEF) by either multigated acquisition scan (MUGA) or echocardiogram (ECHO). Ejection fractions ≤50% and the absence of any significant wall motion abnormality should be documented. Patients must have adequate cardiac function to participate in this trial. Patients with known cardiac history should have a left ventricular ejection fraction > 50% (as determined by MUGA scan or ECHO) prior to enrolment in this trial and cardiac clearance by a consultant cardiologist for major surgery and cancer therapies is required. **This procedure does not need to be repeated if completed within 42 calendar days prior to registration.**
16. Female patients of childbearing potential should have pregnancy excluded by urine or serum beta-HCG testing within 7 calendar days prior to registration and 7 calendar days prior to treatment. The screening pregnancy test does not need to be repeated prior to treatment if the test is within 7 calendar days to treatment. The criteria for postmenopausal status are defined as:
    - Bilateral surgical oophorectomy, or
    - No spontaneous menses >1 year, or
    - No menses for < 1 year with FSH and oestradiol levels in postmenopausal range, according to institutional standards.
17. Upper Gastro-intestinal Multi Disciplinary Team meeting discussion. Please refer to your group specific appendix for local timelines for this meeting to happen.

9.3 Patient Registration:

The patient must be registered in the trial within 28 calendar days from the date of screening visit. The investigator (or designated trial personnel) must check that the eligibility criteria are met before and complete the patient registration form. The patient registration form must be sent to the Cancer Trials Ireland Office. The registration form will be checked at Cancer Trials Ireland and once all information has been verified, Cancer Trials Ireland will register the patient in the trial and email confirmation of registration to the site with the unique patient number and treatment assignment.

9.3.1 Post-Registration Visit /Pre-Treatment Visit Assessments:

1. Blood sample and collection of surplus diagnostic paraffin embedded tumour tissue for exploratory analyses, if not already obtained prior to registration (For SJH patients only, see section 5)
2. Oncology/ Radiation Oncology pre-treatment visit
3. Physical examination (including ECOG performance status, vital signs and weight).
4. Full blood count (FBC): haemoglobin, white cell count, neutrophils and platelets.
5. Serum biochemistry, Renal, Liver and Bone profile: sodium, potassium, creatinine, BUN/Urea calcium, magnesium, chloride, bicarbonate (if possible), phosphate, lactate dehydrogenase (LDH), total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and serum albumin.
6. Creatinine clearance should be calculated using the using the Cockcroft-Gault Formula (Appendix M). If the calculated creatinine clearance is below 60ml/min or serum creatinine

is above the local upper limit of normal, a formal assessment of glomerular filtration rate (GFR) should be performed.
7. Coagulation blood tests: only if clinically indicated
8. Review concurrent medications and adverse events
9. Simulation for radiotherapy if patient is randomised to Arm B only. A date for simulation will be given post Radiation Oncology Visit.
18. Female patients of childbearing potential should have pregnancy excluded by urine or serum beta-HCG testing within 7 calendar days prior to treatment. Note the screening pregnancy test does not need to be repeated prior to treatment if the test is within 7 calendar days to treatment.

Treatment should commence within 21 calendar days (+3 days window is allowed) of registration unless discussed with the Chief Investigator.

9.4. Assessments required during trial treatment (for both treatment arms)

The following assessments should be performed on, or within 3 calendar days prior to, day 1 of each cycle of treatment unless otherwise stated. (exception for C1D1 where post registration assessments do not need to be repeated if performed within 7 calendar days prior to D1 visit)

1. Capecitabine compliance check (Arm A: MAGIC patients only at beginning of Cycle2, Cycle3 and at End of Neoadjuvant Treatment visit).
2. Vitals and weight
3. Clinical history and physical examination, including ECOG performance status should be performed on or within 5 calendar days prior to day 1 of each cycle.
4. Concurrent medication and adverse event evaluation
5. Full blood count (FBC): haemoglobin, white cell count, neutrophils and platelets.
6. Serum biochemistry, Renal, Liver and Bone profile: sodium, potassium, creatinine, creatinine clearance, BUN/Urea, calcium, magnesium, chloride, bicarbonate (if possible), phosphate, lactate dehydrogenase (LDH), total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and serum albumin.
7. Coagulation blood tests: only if clinically indicated
8. Quality of life (EORTC QLQ C30 (Including EORTC QLQ-OES 18)) after preoperative neoadjuvant chemotherapy or chemoradiation and prior to surgery.

9.5. Assessments required within 8 weeks post last dose of neoadjuvant treatment (for both treatment arms).

Please refer to group specific appendix if local standard of care differs from these timelines.

1. A restaging CT or CT-PET scan of the thorax, abdomen and neck (as per institutional standard practice) will be performed after completion of trial treatment A restaging OGD to assess endoscopic response
2. Re-discussion at Gastro–Intestinal MDT Conference
3. Visit to specialist surgeon for consideration for progression to surgery and anticipated date for surgery. Patients should aim to have surgery within 3-10 weeks of completing neo-adjuvant treatment, unless discussed with the Chief Investigator.
4. Clinical history and physical examination (including ECOG performance status, ASA grading, assessment of any treatment related toxicity and weight).
5. Full blood count (FBC): haemoglobin, white cell count, neutrophils and platelets.
6. Serum biochemistry, Renal, liver and bone profile: sodium, potassium, creatinine, BUN/Urea calcium, magnesium, chloride, bicarbonate (if possible), phosphate, lactate dehydrogenase

(LDH), total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and serum albumin.
7. Coagulation screen (INR and/or PT assessments)
8. Quality of life (EORTC QLQ C30 (Including EORTC QLQ-OES 18)) will be performed post-treatment and pre-surgery

9.6 Surgery

The details of surgery performed, histology and response to neo-adjuvant treatment should be reported in the eCRF. The pathology results, staging and Mandard tumour regression grade along with residual tumour classification should be reported in the eCRF.

9.7 Assessments required post-surgery (for both treatment arms)

1. An initial post-op visit will occur within 2 weeks -1 month post-discharge from hospital post-surgery or sooner as patient's condition determines.
2. After the initial post-operative visit to the trial team, Arm A patients will be assessed for adjuvant chemotherapy as per protocol (Table 23 or 24) and will be referred to the treatment oncologist for completion of treatment. Follow-up visits for Arm A patients will occur concomitantly during their adjuvant treatment.
3. Follow-up visits at the trial centre will occur at 3 months, 6 months, 9 months and 12 months for the 1st year and 6 monthly thereafter for a maximum of 5 years or until progression of disease is documented or death or until the last patient has completed 18 months follow-up, whichever occurs earlier (Table 21 Study Assessments and Procedures Post-Surgery). During these visits, the following will be evaluated:
    - Clinical history and physical examination (including, ECOG performance status and resolution of any treatment related toxicity, weight).
    - Assessment of operative and treatment related toxicity. All post-operative complications will be captured for up to 90 days after surgery and graded according to the Clavien-Dindo classification system and the criterial established by the Esophagectomy Complications Consensus Group (Appendix I).
    - Quality of life (EORTC QLQ C30 (Including EORTC QLQ-OES 18)) will be performed during follow up at 3 months, 6 months, 1 year, 2 years and 3 years.* Routine blood tests are not required unless clinically indicated.
4. Patients who have completed 5 years of follow-up per Table 21 will be followed up for survival every 6 months thereafter until death or until the last patient has completed 18 months follow-up, whichever occurs earlier.

** Year 2 and 3 assessments are not applicable if they are due post End of Trial.*

9.7.1 Disease Assessments (for both treatment arms)

A CT or CT-PET scan (as per institutional standard practice) and OGD should be carried out at 1, 2 and 3-years post registration (and as clinically indicated thereafter). Refer to Table 22 for both treatment arms. This visit can be combined with one of the standard post-surgery visits. Please refer to the group specific appendix for special considerations in participating countries and their standard of care.

9.8 Survival Follow-up

Survival follow-up assessments relate to both treatment arms.
Progression of disease should be documented by appropriate imaging.

In patients who have progression of disease either on or after trial treatment or patients who have moved to survival follow-up for other reason, survival follow up should still occur at 3 months, 6 months, 9 months and 12 months post–surgery or (withdrawal from trial treatment if surgery did not take place) for the first year and 6 monthly thereafter until death or the end of the trial, whichever occurs earlier.

Patients who have completed 5 years of follow-up per Table 21 will be followed up for survival every 6 months thereafter until death or the end of the trial, whichever occurs earlier.

The end of trial is defined as when the last patient enrolled in the trial has completed 18 months follow-up, i.e. 18 months post randomisation.

In this case, follow-up may occur by telephone, and where possible, the following should be documented:

- Resolution of any treatment related toxicities due to treatment received within this trial, if ongoing at the time the patient was withdrawn from the trial.
- Disease progression
- Any post-progression/ 2nd line cancer treatment (treatments or regimens used) should be recorded on the Anti-Cancer Treatment eCRF.
- If a patient is lost to follow-up this should be documented and data reported on the eCRF
- Patients that are removed from the trial due to any reason (i.e., toxicity, delays, etc.) but still go on to continue standard trial (CROSS or MAGIC/FLOT) therapy off trial, should still have this information captured on the Anti-Cancer Treatment eCRF.

10. Statistical considerations

10.1 Statistical Considerations

The aim of this trial is to compare 3-year overall survival (OS) for neoadjuvant and adjuvant chemotherapy (Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction exclusively in patients defined as high-risk for relapse, and encompassing strict surgical quality assurance and quality of life assessment sooner.

Regarding expectations for 3-year survival, the results of the CROSS-trial and FLOT4 provide useful information, though the studies are not directly comparable to this trial. Three-year OS was 57% for FLOT in the FLOT4 trial (and 48% for ECF/ECX), and 3-year survival was 59% in the CROSS-trial. The results of the first futility analysis for this trial provided estimates of 52% and 57% for the CROSS protocol and Modified MAGIC regimen respectively (yielding a hazard ratio of 0.98 with 95% confidence interval of 0.62 to 1.53). It might therefore be expected that the neoadjuvant and adjuvant chemotherapy arm (Modified MAGIC or FLOT regimen) would have a 3-year OS of 57%. Based on the CROSS-trial and the results of the first futility analysis, a reasonable expectation for 3-year OS for the CROSS protocol in adenocarcinoma of the oesophagus and oesophago-gastric junction is 53%. The comparison of the two arms will thus be performed using non-inferiority testing with a view to demonstrating that the 3-year OS of the neoadjuvant and adjuvant chemotherapy is not inferior to neoadjuvant chemoradiation.

Overall survival will be calculated from randomization to death from any cause. Disease-free survival will be calculated from randomization to the first event (i.e. local recurrence or progression, distant recurrence, or death from any cause).

Kaplan Meier methods and Cox proportional hazards regression will be used to analyse data where the outcome variable is time until occurrence of an event. Categorical data will be analysed using chi squared tests and Fisher's Exact tests as appropriate.

10.2. Study Design

This is a multicentre phase 3 open-labelled, randomised controlled trial. Patients will be randomized in a 1:1 fashion between the two arms.

10.3. Stratification

It is not necessary to stratify the randomization for investigative site or for any baseline patient/disease characteristic.

10.4. Analysis of populations

The primary analysis will be performed on an intention to treat (ITT) basis, that is, for all patients randomised into the trial, regardless of whether they received treatment or what treatment they received.
A per-protocol analysis, excluding patients who did not sufficiently comply with the protocol (in terms of exposure to treatment, availability of measurements and major protocol violations) will supplement the ITT analysis as a secondary analysis.

10.5. Study Endpoints

10.5.1 Primary end point

The primary endpoint is overall survival which will be calculated from the date of randomization to the date of death from any cause. Patients lost to follow up or those with no death recorded on the day the database is frozen, will be censored on the date of last follow up.

10.5.2 Secondary end points

The following are other end points to be evaluated in this trial:

- Clinical and endoscopic response rate
- Tumour Regression Grade
- Surgical resection rate ((i) Resectability & (ii) Pathologic R0 resection)
- Post-operative pathology staging
- Disease-free survival
- Time to treatment failure
- Site of treatment failure
- Toxicity
- Post-operative Complications
- Health related quality of life (EORTC-QLQ)

Over 80% of patients who relapse after oesophago-gastric surgery do so within 2 years and therefore we propose that statistical considerations are based on 3-year overall or disease-free survival.

10.6 Multivariate analyses

Multivariate analyses will be performed to evaluate the effect of known prognostic factors or potential prognostic factors on outcomes observed.

10.7 Sample Size Considerations

10.7.1 Original Sample Size Calculation for Non-Inferiority Testing

A total of 628 patients (314 patients per treatment arm) will be sufficient to provide 80% power to test the non-inferiority of neoadjuvant and adjuvant chemotherapy versus neoadjuvant chemoradiation, assuming the expected 3-year OS for both arms is 53%, and using a non-inferiority margin of 8.5% (corresponding to a non-inferiority hazard ratio of 1.275 where neoadjuvant and adjuvant chemotherapy is the numerator) and an alpha level of 5%. The data will be analysed 18 months after the last patient enters the trial. The period over which patients are to be recruited is considered to be 6 years for the purposes of the sample size calculation, and the proportion of patients lost during follow-up is assumed to be 5%. These calculations are based on the exponential survival function and the assumption that the hazard rates are proportional [(34)].

10.7.2 Revised Sample Size Calculation for Non-Inferiority Testing

The sample size was revised based on the results of the first futility analysis (See Sections 10.1 and 10.9).

A total of 540 patients (270 patients per treatment arm) will be sufficient to provide 80% power to test the non-inferiority of neoadjuvant and adjuvant chemotherapy versus neoadjuvant chemoradiation, assuming the expected 3-year OS rates are 57% and 53% respectively, and using a non-inferiority margin of 5% (corresponding to a non-inferiority hazard ratio of 1.16 where neoadjuvant and adjuvant chemotherapy is the numerator) and an alpha level of 5%. The data will be analysed 18 months after the last patient enters the trial. The period over which patients are to be recruited considered to be 6 years for the purposes of the sample size calculation, and the proportion of patients lost during follow-up is assumed to be 5%. These calculations are based on the exponential survival function and the assumption that the hazard rates are proportional [(34)].

10.8 Planned Methods of Analysis

10.8.1 Overall survival

Survival curves will be generated using the methods of Kaplan and Meier. The overall survival will be expressed as median survival with 95% confidence interval and 3-year survival with 95% confidence interval. Comparisons between the two arms will be made using the hazard ratio and its 95% confidence interval, with non-inferiority demonstrated if the upper bound (UB) of the 95% confidence interval is less than the prespecified margin of 1.16 for non-inferiority (primary analysis).

If the UB of the 95% confidence interval for the hazard ratio is not only less than the non-inferiority margin of 1.16, but is also less than 1 (UB < 1), then there is evidence of superiority in terms of statistical significance at the 5% level. In this case it is acceptable to calculate the p-value associated with a test of superiority and to evaluate whether this is sufficiently small to reject convincingly the hypothesis of no difference between treatment arms. There is no multiplicity argument that affects this interpretation because, in statistical terms, it corresponds to a simple closed test procedure.

Stepwise multivariate Cox regression analysis will be used to calculate corrected hazard ratios and 95% confidence interval. This multivariate analysis will incorporate the known prognostic factors to ensure the comparison arms are balanced.

Forest plots with tests of homogeneity will be created to display the treatment effects for a variety of different prognostic groups.

10.8.2 Adverse event assessments

The proportion of patients experiencing grade 3 or 4 toxicity will be compared on a regimen basis using the chi-squared test, Fisher's Exact test will be used when expected cell frequencies are less than 5. The chi-squared test for trend will also be used to compare all toxicity scores.

10.8.3. Quality of Life

The functional and symptomatic scales of the EORTC quality of life questionnaires will be examined by calculating the differences in measurements from baseline. The functional and symptomatic scores will be calculated using the standard EORTC recommended methods. Differences from baseline will be compared between arms of the trial using independent sample t-tests. Large numbers are anticipated in this trial, so it is unlikely that non-parametric methods will be performed. Adjustments for demographic and patient history will be made through multiple regression analysis.

All calculations will use 2-sided p-values and a threshold of 0.05 will be used to indicate statistical significance.

10.8.4. Other Endpoints

Kaplan-Meier survival curves will be used to analyse disease-free survival and time to treatment failure, and comparisons between treatments will be made using the log-rank test. A Cox regression model will be used to assess and control for prognostic factors of interest. Response rates, tumour regression grade, surgical resection rate, and post-operative pathology staging will be analysed using chi-squared tests and Fisher's Exact tests as appropriate. Site of treatment failure will be analysed descriptively.

10.8.5. Exploratory Analysis

The analysis of the primary and secondary efficacy endpoints will be repeated to explore treatment differences between CROSS and each of the FLOT and MAGIC regimens. As the trial is not powered to investigate these treatment differences, care should be taken in evaluating the results to avoid misleading conclusions.

10.9 Missing Data

There will be no imputation of missing values.

Patients whose eligibility for the study cannot be determined because of missing data will be considered ineligible for the study and will not be included in the Per-Protocol analysis, but will be included in the Intention To Treat analysis.

The impact of missing data on the statistical analysis of the primary and secondary outcome measures (mainly time-to-event variables) is expected to be minimal, assuming every reasonable effort is made to follow patients as per protocol.

For patients with missing or partial AE onset dates, the most conservative approach will be taken in determining treatment emergence.

10.10 Interim Analyses and Statistical Monitoring

Interim futility analyses will be based on the rule of Freidlin et al (2010), with a Linear 20% Inefficacy Boundary (LIB20). This rule provides the opportunity to terminate early for evidence that the

experimental arm is unacceptably inferior to the control arm, but protects against aggressive early termination for treatment effect sizes smaller than planned. There will be an early 'harm' look based on 25% of information (74 deaths), and if the lower bound (LB) of the Confidence Interval for the hazard ratio is >= 1.275 then the trial will be stopped for futility as neoadjuvant and adjuvant chemotherapy is unacceptably inferior to neoadjuvant chemoradiation (see Section 10.1 for results of first futility analysis). A second interim look for futility will be performed after 50% of information is available (140 deaths). If LB >= 1 then the trial will be stopped for futility (non-inferiority of neoadjuvant and adjuvant chemotherapy is no longer expected at the end of the trial). The results of the futility analyses will be reported to the Data Safety Monitoring Committee (see Section 11.4.2). The results of the interim analyses will also be used to check the assumptions of the sample size calculation in Section 10.7.2.

The trial statistician can be called on to examine the data for anomalies and outliers, such as too few or too many events. Queries will be raised by the trial coordinators in such situations and communication with the clinical teams will take place. In addition, statistical monitoring of unusual data and inconsistent data will take place. Again, these will raise queries via the trial coordinators.

11. Safety

Timely, accurate and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and are mandated by regulatory agencies worldwide.

11.1 Adverse Event, Serious Adverse Event and Post-operative complications; Definitions, Classifications and Periods of Observation

11.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product (definition per International Conference on Harmonization [ICH]).
This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Monitoring of Adverse Events and period of observation

Adverse events, both serious and non-serious, and deaths that occur during a patient's trial participation will be recorded on the case report form. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

All AEs meeting "serious" criteria occurring in each patient should be reported up to 30 days after the last dose of trial drug has been received. Any SAEs occurring in patients after the 30 days of active follow up, which are deemed by the investigator to be causally related to trial treatment received during the trial should be forwarded to the Cancer Trials Ireland Pharmacovigilance Unit as outlined above. These cases will be acknowledged by facsimile/ email as above.

Procedure for Recording Adverse Events

Adverse Events (AE) that are new, or worsening will be recorded on the AE eCRF from the time of informed consent up to 30 days after the last dose of trial drug has been received.

AEs and Concomitant Medications should be recorded as follows:
Arm A: From time of informed consent until 30 days post last dose of neo-adjuvant treatment and again from the first cycle of adjuvant chemotherapy until 30 days post last dose of adjuvant treatment.
Arm B: From time of informed consent until 30 days post end of the last dose of chemotherapy or radiation therapy.

AEs must be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (Appendix C/J). In cases where these criteria do not apply, intensity should be defined according to the general clinical description of grades as per CTCAE.

Those meeting the definition of serious adverse events must be reported using the SAE Report Form.

All post-operative complications will be recorded on the Post-Operative eCRF for up to 90 days after surgery. The highest severity complication will be graded according to the Clavien-Dindo classification system and the Esophagectomy Complications Consensus Group (Appendix I).

See Appendix N for further guidance on event time points (neo-adjuvant, post-operative and adjuvant treatment phases).

Abnormal test results

Test Abnormalities Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. Electrocardiogram (ECG), radiological scans, vital signs measurements), including those that worsen from baseline, considered **clinically significant** in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).

11.1.2 Serious Adverse Event

A serious adverse event as defined by ICH is any untoward medical occurrence in a patient or clinical investigation patient administered with a pharmaceutical product and which does not necessarily have to have a causal relationship to the treatment.

The serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalisation* or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Significant medical hazard**

***** If hospitalisation is the serious criterion this means 'in-patient hospitalisation', i.e. a patient has been admitted to hospital, and therefore, visits on an out-patient basis or without admission as an in-patient are excluded.

****Note:** Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events

may not be immediately life threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact. The SAE criterion 'medically significant' or 'other significant medical hazard' applies to these types of events.

Clarification on the definition of "severe" and "seriousness"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Disease-related events or outcomes

The term 'Disease Progression' should not be reported as an SAE. Disease Progression will be recorded as an outcome in the CRF.

All signs and symptoms that fulfil the criteria of seriousness are to be reported as SAEs including those suspected as progression of the underlying disease under study. In such cases, suspicion or confirmation of disease progression are to be noted in the comment section of the SAE report form.
Also, if the rate of disease progression is higher than would normally be expected for the patient population or if the investigator considers that there was causal relationship between the study treatment and/or the protocol design/procedures and the disease progression, then this must be reported as an SAE.

Death due to disease progression is not to be reported as an SAE but recorded as an outcome in the CRF. The symptom of disease progression which caused death should instead be reported as an SAE. Refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for recording of Death due to disease progression that cannot be attributed to a CTCAE term associated with Grade 5.

New Primary Cancer
Any new primary cancer (malignancy unrelated to the patient's underlying disease under study or its progression) must be reported as an SAE.

Admissions for planned surgery/procedures
Admissions for elective/ planned surgery or procedure (e.g. a biopsy) following the start of study treatment should not be reported as SAEs.
Admission for surgery due to an AE must be reported as an SAE.

Overdose
Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported as AE/SAE regardless of sequelae.

11.1.3 Procedures for Recording and Reporting Serious Adverse Events

All AEs meeting "serious" criteria occurring in each patient should be reported from the time of informed consent up to 30 days after the last dose of trial drug has been received.

The Investigator will submit to the Cancer Trials Ireland Pharmacovigilance unit, using the SAE report forms provided, all Serious Adverse Events in the trial regardless of whether causality with the administration of trial drug is suspected by the investigator. The Investigator will transmit the SAE reports by facsimile or email to Cancer Trials Ireland immediately i.e. defined as within 24 hours of a member of the research team becoming aware of the event(s). See Appendix N for further guidance on event time points (neo-adjuvant, post-operative and adjuvant treatment phases)

Any SAEs occurring in patients after 30 days of the last dose of trial drug, which are deemed by the investigator to be causally related to trial treatment (chemotherapy/radiotherapy) should be forwarded to the Cancer Trials Ireland Pharmacovigilance Unit as outlined above. These cases will be acknowledged by facsimile/ email. An adverse event is considered associated with the use of the IMP/treatment if the attribution is definitely, probably or possibly related.

Please refer to section 11.2 for reporting of SAEs during the post-operative period (90 days post-surgery).

All SAE reports to be sent immediately to:

Cancer Trials Ireland **PHARMACOVIGILANCE UNIT**
Email: pharmacovigilance@cancertrials.ie
Fax: +353 (0)1 6697869

Cancer Trials Ireland will acknowledge receipt of the SAE within one business day by facsimile/ email to the Investigator.

All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es). Information not available at the time of the initial report e.g. pending lab results must be documented on a follow-up SAE report form. Follow-up information should be sought and submitted as it becomes available. The follow-up information should describe whether the event has resolved or persists, if and how it was treated and whether the patient continues on trial or has been withdrawn from treatment.
If unsure whether an event meets seriousness criteria, please contact the Pharmacovigilance unit at the above email address who will deal with your query and advise on specific reporting requirements.

11.1.4 Sponsor Responsibilities:

Cancer Trials Ireland or designee will perform expedited adverse event reporting for the study according to the applicable regulatory guidelines. Cancer Trials Ireland or designee will submit local SUSARs on an expedited basis to the local regulatory authority, other Competent/ Regulatory Authorities involved and concerned Ethics Committees (EC).

Cancer Trials Ireland or designee will send Annual Development Safety Update Reports (DSURs) to the concerned regulatory authority(ies) and Ethics Committee(s).

Cancer Trials Ireland or designee will inform participating investigators of SUSARs reported for the trial or for other trials using the same investigational medicinal product for which Cancer Trials Ireland is acting as study sponsor. The information will be provided in a format (such as reports or line listings) and time interval as warranted by the nature of the trial and the volume of SUSARs generated.

Determining Expectedness
Cancer Trials Ireland will assess the expectedness of each reported serious adverse reaction in order determine if it is a Suspected Unexpected Serious Adverse Reaction (SUSAR).

A SUSAR is any adverse reaction for which the nature or severity is not consistent with the applicable product information (i.e. Summary of Product Characteristics (SmPC)).

The current approved SmPC submitted with the trial application or substantial amendment will be used to determine expectedness.

For an IMP with a marketing authorisation (commercial agent), the expectedness of an adverse event will be determined by whether or not it is listed in the approved RSI source (SmPC).

For this trial, all drugs used will be commercial stock. The current versions of the following summary of product characteristics (SmPC) documents are to be used to assess the expectedness of the IMP's in the trial:

- Summary of Product Characteristics: Cisplatin
- Summary of Product Characteristics: Epirubicin
- Summary of Product Characteristics: 5-fluorouracil
- Summary of Product Characteristics: Capecitabine
- Summary of Product Characteristics: Carboplatin
- Summary of Product Characteristics: Paclitaxel
- Summary of Product Characteristics: Oxaliplatin
- Summary of Product Characteristics: Leucovorin
- Summary of Product Characteristics: Docetaxel

11.1.5 Associated with the Use of the IMP/ treatment

Relationship to each trial product/treatment administered will be determined by the investigator.

An adverse event is considered associated with the use of the IMP/treatment if the attribution is definitely, probably or possibly related.

11. 2 Reporting of post-operative complications

All post-operative complications will be recorded on the Post-Operative Complications eCRF for up to 90 days after surgery. The highest severity complication will be graded according to the Clavien-Dindo classification system and the Esophagectomy Complications Consensus Group (Appendix I).

Post-operative complications that meet SAE criteria should be reported as SAEs if they occur within the SAE reporting period (please refer to section 11.1.2 under 'Procedures for Documenting and Reporting Serious Adverse Events').

If post-operative complications occur outside of the SAE reporting period in section 11.1.2 then they should only be reported as SAE's if they meet **both** of the following two criteria:

- The event meets SAE criteria as per section 11.1.2
- The event is deemed causally related to the trial treatment (chemo/radiotherapy) by an investigator.

All post-operative mortality events (deaths) should be reported as SAEs (**90 days post-operative**), regardless of cause.

See Appendix N for further guidance on event time points (neo-adjuvant, post-operative and adjuvant treatment phases).

11.3 Procedures for Documenting and Reporting Pregnancies

Female patients or male patients' partner's pregnancy (as applicable) must be reported to Cancer Trials Ireland by the investigator within 24 hours of the trial site becoming aware of the event, by facsimile/email using the Pregnancy Report Form located in the Investigator Site File (ISF).

Cancer Trials Ireland will acknowledge receipt of this form by facsimile/ email. Any patient who becomes pregnant during the trial must be promptly withdrawn from the trial following withdrawal procedures outlined in protocol section 4.8. The pregnancy will be monitored closely until the birth. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

11.4 Study Review

The Cancer Trials Ireland Clinical Lead is the Sponsor's designated medical overseer for this trial and will be responsible on an ongoing basis to review and assess any concerns particularly safety issues that may arise in this trial, in compliance with Cancer Trials Ireland SOP – Medical Oversight and Benefit/ Risk Monitoring.

The trial will be allocated to an appropriate Cancer Trials Ireland Disease-Specific Subgroup (DSSG). The progress and conduct of the trial will be reviewed three to four times per year by the Chief Investigator and participating investigators during the Cancer Trials Ireland DSSG meetings. The main responsibility of the Cancer Trials Ireland DSSG is to review the ongoing status of the trial including planned and actual recruitment targets, trial updates presented by the Chief Investigator or designee, including recommendations made by the Trial Steering Committee (TSC) and Data Safety Monitoring Board (DSMB). The group will consider the progress of the trial and make recommendations to the Cancer Trials Ireland Executive Committee and TSC, where necessary. The outcome of the DSSG meeting and review will be documented in writing and distributed to all DSSG members.

11.4.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be established to oversee and review on an ongoing basis the trial progress and recruitment, patients' safety and monitoring, adherence with the protocol, review of information from related research, and implementation of recommendations from the trial Sponsor and external bodies (e.g. DSMB). The role, membership, responsibility and activities of the TSC will be documented in the TSC Charter. The TSC is the primary group responsible for scientific integrity of the Neo-AEGIS Study. The outcome of the TSC meetings will be documented in writing. Recommendations which may have an impact on the trial design, recruitment and/or patient's safety and monitoring will be communicated to the Cancer Trials Ireland DSSG at each scheduled meeting.

11.4.2 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) is deemed to be necessary for this trial. It will be established to ensure that patients entered into this trial are not disadvantaged compared to standard treatment. The DSMB will consist of independent members and will be chartered to review safety and efficacy data and make recommendations regarding trial continuation, termination, or modifications to the trial design to the Sponsor and in other events as indicated in section 12.8. The DSMB roles, responsibilities, meetings and logistics will be outlined in the trial DSMB Charter. It is expected that the first DSMB meeting will be scheduled after 50 patients have been enrolled in the trial and then

biannually. The DSMB will provide recommendations during the trial conduct to the TSC and Cancer Trials Ireland. The TSC and Cancer Trials Ireland (headed by Clinical Lead) will review the information and the recommendations of the DSMB and make a decision regarding the implementation of the recommendations at each time point. The implementation of any DSMB recommendation is solely the responsibility of the Sponsor who is also free to neglect (in whole or in part) recommendations of the DSMB. In this case, the Sponsor should provide adequate rationale in writing to the DSMB, the relevant National Competent Authority(ies) and Ethics Committee(s) with the rationale for neglecting the recommendations of the DSMB.

Any key documentation and meeting minutes related to the trial review, DSSG, TSC meetings and DSMB recommendations will be retained by the Sponsor in compliance with section 12.9.3 Record Retention.

12. Administrative Responsibilities

12.1 Good Clinical Practice (CPMP/ICH/135/95)

The trial will be conducted in accordance with the EU Directive 2001/20/EC and International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the trial treatment as described in the protocol and/or SmPC. Essential clinical documents will be maintained to demonstrate the validity of the trial and the integrity of the data collected. Master files should be established at the beginning of the trial, maintained for the duration of the trial and retained according to the appropriate regulations.

12.2 Ethical considerations

The trial will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (current edition located at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).
The competent authority/ ethics committee will review all appropriate trial documentation in order to safeguard the rights, safety and wellbeing of the patients. The protocol, summary of product characteristics, informed consent, written information given to the patients, safety updates, annual progress reports and any revisions to these documents will be provided to them by the Sponsor. The trial will only be conducted at sites where their full approval has been obtained.

12.3 Patient information and informed consent

After the trial has been fully explained, written informed consent will be obtained from the patient prior to trial participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirements.

12.4 Patient confidentiality

In order to maintain patient privacy, all case report forms, trial drug accountability records, trial reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant auditor(s) from regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the case report forms and to audit the data collection process. The patient's confidentiality will be maintained and patient names will not be disclosed.

12.5 Protocol compliance

The investigator will conduct the trial in compliance with the approved protocol. Changes to the protocol will require written competent authority/ ethics committee approval/favourable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The Sponsor will submit all protocol modifications to the competent authority/ethics committee for review in accordance with the governing regulations.

12.6 Monitoring, Auditing, and Inspecting

The Sponsor will conduct site monitoring in accordance with the trial monitoring plan.
This site monitoring will be an ongoing activity from the time of initiation until trial closeout and will comply with EU directive 2001/20/EC and ICH GCP (CPMP/ICH/135/95) regulations. The trial will be monitored by regular site visits and telephone calls to the investigator. During site visits, the monitor should review original patient records, eCRF, trial treatment records and document retention. Additionally, the monitor should observe compliance with trial procedures and will discuss any problems with the investigator. All site monitoring visits will be documented and the reports will be filed.

During the course of the trial the Sponsor or competent authorities may conduct site audits or inspections. The investigator will provide direct access to source data/documents for trial related monitoring, audits, competent authority/ ethics committee review and regulatory inspections.

12.7 Drug accountability

All drugs used in this trial will be commercial stock and will be sourced through the standard hospital procedures. All trial drugs will be stored as per the current version of the products' SmPC (Summary of Product Characteristics) and the standard hospital procedures. Pharmacy will maintain dispensing records and temperature logs as per hospital pharmacy standard operating procedures.

Capecitabine prescriptions must be documented in the physician's order sheets or by retention of a copy of the prescription, if not dispensed directly by the hospital pharmacy. Compliance with capecitabine dosing will be assessed through questioning the patient during the visits and documented in the source documents.

12.8 Premature closure of the trial

This trial may be prematurely terminated, if in the opinion of the investigator or the Sponsor, there is sufficient reasonable cause. Written notification documenting the reason for trial termination will be provided to the investigator or the Sponsor by the terminating party.
Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the trial treatment
- New information that becomes available regarding efficacy/risks of treatment
- On recommendation of the DSMB

Should the trial be closed prematurely, all trial materials must be returned. The competent authorities and ethics committee will be notified by the Sponsor according to the regulatory guidelines.

12.8.1 Accrual based early stopping guidelines

The summary timelines for this protocol are as follows: the trial is expected to take approximately 8.5 years to accrue 540 patients. Failure to accrue patients at a predefined minimum rate will result in the trial being terminated early. The DSMB will have the authority to recommend to the TSC and the Sponsor, Cancer Trials Ireland, the discontinuation of the trial in the event of the patients being accrued to the trial at an unacceptable rate.

12.9 Data Management

Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on case report forms will be included on the site delegation log.
Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and trial staff are responsible for maintaining a comprehensive and centralized filing system of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed case report forms, informed consent forms, and patient identification list

Study files containing the protocol with all amendments, copies of pre-trial documentation, and all correspondence to and from the Sponsor and institutional review board. In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No trial document should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the trial records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

12.9.1 Recording of data

The trial will be conducted using a paper Patient Registration Form and electronic based CRFs (eCRF). The Patient Registration Form must be printed legibly by an authorised staff member. A copy will be retained in the investigator's site file or patient chart. Case Report Forms and all original data should be readily available for review during scheduled monitoring visits.

Per ICH-GCP, any change or correction to a CRF should be dated, initialled and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained).

eCRF completion guidelines will be provided to each site and any questions about the appropriate location on the CRF for recording specific information should be directed to the monitor.

12.9.2 Data Quality Assurance

All data will be reviewed for completeness and logical consistency by the Monitors and Data Management team in HRB Clinical Research Facility. For the eCRF-Data queries will be generated via the electronic data capture system to correct or clarify data or request missing information. The designated site staff will be required to respond to these queries in accordance with data entry and

data query timelines for the trial. For the paper CRF (Patient Registration Form only) -Data queries will be generated for the investigational site as required to clarify data or request missing information. The designated site staff will be required to respond to these queries and send them back to the Cancer Trials Ireland / HRB Clinical Research Facility after they have been reviewed and signed by the investigator/ delegated staff member. Any amended information will then be entered in the database. A copy of the signed query form should be retained with the CRF binder on site.

The investigator will be responsible for the review and sign off of data entered and corrected at their site.

12.9.3 Record Retention

An investigator site file will be provided by Cancer Trials Ireland for all required trial documents. The investigator will maintain all trial records according to ICH/GCP and applicable regulatory requirement(s). The Sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion. However, this will extend to 25 years due to changes in the law which will apply from 2021. Cancer Trials Ireland as Sponsor will notify investigators when they are no longer required to maintain the files. If the investigator withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept the responsibility and this must be documented in writing to Cancer Trials Ireland.

12.10 Publication Policy

Publication of trial finding and use of information:
All information provided by Cancer Trials Ireland relating to this trial or the investigational agent, and not previously published, is considered confidential and proprietary. This confidential information shall remain the sole property of Cancer Trials Ireland, and shall not be disclosed or used (except in the performance of this trial) without prior written authorisation.

No publication, abstract, or presentation of any aspect of the trial shall be made without the approval of Cancer Trials Ireland. A predetermined procedure will be used to determine the authorship list of any publication or presentation, taking into account participation in the leadership, design and conduct of the trial as well as patient accrual.

Access to the data or results held by Cancer Trials Ireland Data Management or the Data Management team in HRB Clinical Research Facility, Galway will not be allowed prior to final reporting unless specified in the protocol or unless an exceptional authority has been given by the Cancer Trials Ireland Executive.

12.11 Indemnity

Adequate indemnity cover for the protocol will be confirmed by the Sponsor.

13. Appendices

APPENDIX A: References

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capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol. 2017;35(suppl; abstr 4004).
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44. Tucker SL1, Liu HH, Wang S, Wei X, Liao Z, Komaki R, Cox JD, Mohan R. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys. 2006 Nov 1;66(3):754-61. Epub 2006 Sep 11.

APPENDIX B: Tumour Regression Grade

Tumour Regression Grade	
1	TRG 1 (complete regression) showed absence of residual cancer and fibrosis extending through the different layers of the esophageal wall
2	TRG 2 was characterized by the presence of rare residual cancer cells scattered through the fibrosis
3	TRG 3 was characterized by an increase in the number of residual cancer cells, but fibrosis still predominated
4	TRG 4 showed residual cancer outgrowing fibrosis
5	TRG 5 was characterized by absence of regressive changes

Reference [31]

APPENDIX C: Common Toxicity Criteria (NCI CTC) Version 4.03

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX D: Performance Status and ASA Grading

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
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

American Society of Anaesthesiologists (ASA) Grading

ASA Grade	Definition	Mortality (%)
I	Normal healthy individual	0.05
II	Mild systemic disease that does not limit activity	0.4
III	Severe systemic disease that limits activity but is not incapacitating	4.5
IV	Incapacitating systemic disease which is constantly life-threatening	25
V	Moribund, not expected to survive 24 hours with or without surgery	50

ASA PS Classification	Definition	Examples, including but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	
*The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)		

APPENDIX E: Quality of Life (QOL) Form

EORTC QLQ C30 (Including EORTC QLQ-OES 18) Quality of Life Questionnaire *(version 3)*

We are interested is 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.

EORTC QOL Question	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 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:

EORTC QOL Question	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
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

EORTC QOL Question	Not at all	A little	Quite a bit	Very Much
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 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 life?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

Please select which one best suits you, 1= very poor, 7= excellent

29. How would you rate your overall health during the past week?	1	2	3	4	5	6	7
30. How would you rate your overall quality of life during the past week?	1	2	3	4	5	6	7

During the past week

EORTC QOL Question	Not at all	A little	Quite a bit	Very Much
31. Could you eat solid food?	1	2	3	4
32. Could you eat liquidised or soft foods?	1	2	3	4
33. Could you drink liquids?	1	2	3	4
34. Have you trouble swallowing your saliva?	1	2	3	4
35. Have you choked when swallowing?	1	2	3	4
36. Have you had trouble enjoying your meals?	1	2	3	4
37. Have you felt full up too quickly?	1	2	3	4
38. Have you trouble eating?	1	2	3	4
39. Have you trouble eating in front of other people?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you had problems with your sense of taste?	1	2	3	4
42. Have you trouble coughing?	1	2	3	4
43. Have you had trouble with talking?	1	2	3	4
44. Have you had acid indigestion or heartburn?	1	2	3	4
45. Have you trouble with acid or bile coming into your mouth?	1	2	3	4
46. Have you had pain when you eat?	1	2	3	4
47. Have you pain in your chest?	1	2	3	4
48. Have you had pain in your stomach?	1	2	3	4

APPENDIX F: UICC / AJCC Cancer Staging 7th edition (2009)

Oesophageal Primary Tumour (T) **

TX: Primary Tumour cannot be assessed.
T0: No evidence of primary tumour
Tis: High Grade Dysplasia
T1: Tumour invades lamina propria, muscularis mucosae, or submucosa
T1a: Tumour invades lamina propria or muscularis mucosae
T1b: Tumour invades submucosa
T2: Tumour invades muscularis propria
T3: Tumours invades adventitia
T4: Tumour invades adjacent structures
T4a: Resectable tumour invading pleura, pericardium, or diaphragm
T4b: Unresectable tumour invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
**(1) At least maximal dimension of the tumour must be recorded and (2) multiple tumours require the T(m) suffix
*** High grade Dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Regional Lymph Nodes (N)*

NX: Regional lymph nodes cannot be assessed
N0; No regional lymph node metastasis
N1: Metastasis in 1-2 regional lymph nodes
N2: Metastasis in 3-6 regional lymph nodes
N3: Metastasis in seven or more regional lymph nodes
*Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastases

Distant Metastasis (M)

M0: No distant metastasis
M1: Distant metastasis: Tumours of lower oesophagus: M1a denotes tumour in celiac nodes, and M1b denotes other sites. For mid-oesophagus there is no M1a but M1b includes non-regional nodal metastases

Adenocarcinoma

Stage	**T**	**N**	**M**	**Grade**
Stage 0	Tis (HGD)	N0	M0	1, X
Stage 1A	T1	N0	M0	1-2, X
Stage 1B	T1 T2	N0 N0	M0 M0	3 1-2, X
Stage IIA	T2	N0	M0	3
Stage IIB	T3 T1-2	N0 N1	M0 M0	Any Any
Stage IIIA	T1-2 T3 T4a	N2 N1 N0	M0 M0 M0	Any Any Any
Stage IIIB	T3	N2	M0	Any
Stage IIIC	T4a T4b Any	N1-2 Any N3	M0 M0 M0	Any Any Any
Stage IV	Any	Any	M1	Any

APPENDIX G: Summary of Product Characteristics

For this trial all drugs used will be commercial stock. The current approved versions of the following summary of product characteristics (SmPC) documents that were submitted with the original clinical trial application are used to assess the expectedness of the IMPs in the trial:

- Summary of Product Characteristics: Cisplatin
- Summary of Product Characteristics: Epirubicin
- Summary of Product Characteristics: 5-fluorouracil
- Summary of Product Characteristics: Capecitabine
- Summary of Product Characteristics: Carboplatin
- Summary of Product Characteristics: Paclitaxel
- Summary of Product Characteristics: Oxaliplatin
- Summary of Product Characteristics: Leucovorin
- Summary of Product Characteristics: Docetaxel

For reference, the SmPCs can be found for individual products on the Irish Health Products Regulatory Authority (HPRA), European Medicine Agency (EMA), the Danish Medicine and Health Authority (DHMA), the electronic Medicines Compendium (eMC) UK website, and the French 'base de données publique des medicaments' websites at the following links:

1. http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine
2. https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine
3. http://sundhedsstyrelsen.dk/en/medicines/find-medicines
4. http://www.medicines.org.uk/emc/
5. http://base-donnees-publique.medicaments.gouv.fr

APPENDIX H: SUMMARY OF RECOMMENDATIONS FOR ANTIEMETICS IN ONCOLOGY:

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline
http://ascopubs.org/doi/pdf/10.1200/JCO.2017.74.4789

APPENDIX I: Post-Operative Complication List

Esophagectomy Complications Consensus Group

Category	Event Description
Pulmonary	Pneumonia -CDC Definitions http://www.cdc.gov/Features/Pneumonia/
	Pleural effusion requiring additional drainage procedure
	Pneumothorax requiring treatment
	Atelectasis mucous plugging requiring bronchoscopy
	Respiratory failure requiring reintubation
	Acute respiratory distress syndrome. (Berlin definition) http://dx.doi.org/10.1001/jama.2012.5669
	Acute aspiration
	Tracheobronchial injury
	Chest tube drainage for >10 days post-op
Cardiac	Cardiac arrest requiring CPR
	Myocardial infarction (WHO Definition) http://dx.doi.org/10.1093/ije/dyq165
	Dysrhythmia atrial requiring treatment
	Dysrhythmia ventricular requiring treatment
	Congestive heart failure requiring treatment
	Pericarditis requiring treatment
Gastrointestinal: Anastomotic Leak Defined as: Full thickness GI defect involving oesophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification	Local defect requiring no change in therapy or treated medically or with dietary modification
	Localized defect requiring interventional but not surgical therapy, e.g., IR drain, stent or bedside opening and packing of incision
	Localized defect requiring surgical therapy
Gastrointestinal: Conduit necrosis/failure requiring surgery	Conduit necrosis focal. Identified endoscopically. Treatment – Additional monitoring or non-surgical therapy
	Conduit necrosis focal. Identified endoscopically and not associated with free anastomotic or conduit leak. Treatment – Surgical therapy not involving esophageal diversion
	Conduit necrosis extensive Treatment – Treated with conduit resection with diversion

Category	Event Description
Gastrointestinal	Ileus defined as small bowel dysfunction preventing or delaying enteral feeding
	Small bowel obstruction
	Feeding J-tube complication
	Pyloromyotomy/pyloroplasty complication
	Clostridium difficile Infection
	GI bleeding requiring intervention or transfusion
	Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7 calendar days post-op
	Pancreatitis
	Liver dysfunction
Urologic	Acute renal insufficiency (defined as: doubling of baseline creatinine)
	Acute renal failure requiring dialysis
	Urinary tract infection
	Urinary Retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter
Thromboembolic	DVT (deep venous thrombosis)
	PE (pulmonary embolus)
	Stroke (CVA)
	Peripheral Thrombophlebitis
Neurologic/ Psychiatric	Other neurologic injury
	Acute delirium http://www.wai.wisc.edu/pdf/phystoolkit/diagnosis/DSM-IV_Criteria_Delirium.pdf (Definitions DSM IV)
	Delirium tremens
Infection	Wound Infection requiring opening wound or antibiotics
	Central IV line infection requiring removal or antibiotics
	Intrathoracic/intra-abdominal abscess
	Generalized sepsis – CDC definition http://www.cdc.gov/nchs/data/databriefs/db62.htm
	Other infections requiring antibiotics
Wound/ Diaphragm	Thoracic wound dehiscence
	Acute abdominal wall dehiscence/hernia
	Acute diaphragmatic hernia

Category	Event Description
Chyle leak Defined as: Milky discharge upon initiation of enteric feeds and/or pleural fluid analysis demonstrating triglyceride level >100 mg/dl and/or chylomicrons in pleural fluid	Chyle leak. Treatment – total parenteral nutrition
	Chyle leak. Treatment – interventional or surgical therapy < 1 liter output/day (Does not include elective insertion of additional surgical or interventional chest drains)
	Chyle leak. Treatment interventional or surgical therapy > 1 liter output/day (Does not include elective insertion of additional surgical or interventional chest drains)
Vocal Cord Injury/Palsy Defined as: Vocal cord dysfunction post-resection. Confirmation and assessment should be by direct examination.	Transient injury requiring no therapy. Dietary modification allowed
	Injury requiring elective surgical procedure, e.g., thyroplasty or medialization procedure
	Unilateral injury requiring acute surgical intervention (due to aspiration or respiratory issues), e.g., thyroplasty or medialization procedure.
	Bilateral injury requiring acute surgical intervention (due to aspiration or respiratory issues), e.g., thyroplasty or medialization procedure.
Other	Reoperation for reasons other than bleeding, anastomotic leak or conduit necrosis
Other	Multiple organ dysfunction syndrome

Note:

1. The total number of post-operative complication(s) must be reported on the trial eCRF (please mark YES/NO).
2. The highest Clavien-Dindo severity grade will be reported on the eCRF
3. The Clavien-Dindo classification of surgical complication can be referenced using the following link: https://www.assessurgery.com/clavien-dindo-classification/

Reference: Dindo D., Demartines N., Clavien P.A.; Ann Surg. 2004; 244: 931-937
Esophagectomy Complications Consensus Group (Low DE, et al . Ann Surg 2015: 262; 286-294)

APPENDIX J: Radiation Toxicity - NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Adverse event	1	2	3	4	5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Weight loss	Weight loss 5 to <10% from baseline; intervention not indicated	Weight loss 5 to <10% from baseline; nutritional support indicated	Weight loss 5 to <10% from baseline; tube feeding or TPN indicated	-	-
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Oesophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Cough	Mild symptoms; non-prescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Lung Infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Dermatitis Radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Pain due to Radiation (refers to skin dermatitis pain)	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Chest Pain – Cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-

Acute coronary Syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal,	Death
White Blood Cell decrease	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Pneumonitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or Non-invasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Chronic Kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Hepatic Failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death
Dyspnoea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

APPENDIX K: Classification of resection margins in oesophageal cancer

Residual tumour classification as determined by the Royal College of Pathology (RCP)

Rx- unknown
R0- No residual tumour
R1- Microscopic Residual Tumour (margins are considered positive when the tumour is located within 1 mm of the cut margin)
R2- Macroscopic Residual Tumour
Not specified

Residual tumour classification as determined by the College of American Pathologists (CAP)

Rx- unknown
R0- No residual tumour
R1- Microscopic Residual Tumour (margins are considered positive when tumour is found at the cut margin of resection)
R2- Macroscopic Residual Tumour
Not specified

APPENDIX L: Guidelines for Endoscopic Regression response grading by endoscopy

Complete response: No evidence of tumour

Partial response: estimated reduction of 50% or greater of tumour.

No response: estimated reduction of less than 50% of tumour

APPENDIX M: CALCULATED CREATININE CLEARANCE FORMULA

Please use the following formula to calculate creatinine clearance for eligibility and at all other trial required visits

Cockcroft and Gault equation: use the following website for calculations

http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

PLEASE ENSURE TO KEEP/PRINT RESULTS AND FILE IN THE PATIENT'S MEDICAL RECORD

APPENDIX N: EVENT REPORTING TIMEPOINTS

<table>
<tr><th colspan="2">Event type / Study time point</th><th>Arm A (modified MAGIC or FLOT)</th><th>Arm B (CROSS)</th></tr>
<tr><td rowspan="4">Adverse Events (AEs)</td><td>Baseline/Pre-treatment</td><td colspan="2">AEs present at baseline which commenced prior to trial participation (informed consent) and have not worsened prior to commencing treatment, should be documented as pre-existing toxicities/conditions and recorded as medical history on the Pre-registration/Baseline CRF only.
Any AEs which are new or have worsened in grade from the date of trial participation (informed consent) should be evaluated per protocol and recorded on the AE CRF.</td></tr>
<tr><td>Neoadjuvant treatment / Pre-surgery</td><td rowspan="3">AEs and Concomitant Medications (CMs) should be evaluated and recorded on the AE and CM CRF from Cycle 1 Day 1 until 30 days post last dose of neo-adjuvant treatment and again from the first cycle of adjuvant chemotherapy until 30 days post-last dose of adjuvant treatment.

From the date of surgery up to 90 days post-surgery any new events which constitute post-operative complications (see protocol Appendix I) should be captured on the post-operative complications CRF as appropriate (see below for further details). Post-op complications do not need to be captured on the AE CRF.</td><td>AEs and CMs should be evaluated and recorded on the AE and CM CRF from Cycle 1 Day 1 until 30 days post last dose of Cycle 5 or last RT treatment (whichever is later).

From the date of surgery up to 90 days post-surgery any new events which constitute post-operative complications (see protocol Appendix I) should be captured on the post-operative complications CRF as appropriate (see below for further details).
Post-op complications do not need to be captured on the AE CRF.</td></tr>
<tr><td>Surgery</td></tr>
<tr><td>Post-operative period</td></tr>
<tr><td>Adjuvant treatment</td><td>N/A</td></tr>
<tr><td colspan="2">Serious Adverse Events (SAEs)</td><td>All events meeting SAE reporting criteria should be reported from the date of trial participation (informed consent) up to 30 days post last dose of any trial drug.

Events which occur >30 days post-last dose of any trial drug that meet SAE reporting criteria <u>and</u> are deemed related to treatment (chemo) by a trial investigator should also be reported.
All deaths should be reported up to 90 days post-operative and 30 days post last dose of adjuvant treatment.</td><td>All events meeting SAE reporting criteria should be reported from the date of trial participation (informed consent) up to 30 days post last dose of Cycle 5 or RT treatment (whichever is later).

Events which occur >30 days post-last dose of any trial drug or RT treatment that meet SAE reporting criteria <u>and</u> are deemed related to treatment (chemo or RT) by a trial investigator should also be reported.
All deaths should be reported up to 90 days post-operative.</td></tr>
<tr><td colspan="2">Post-Op Complications</td><td colspan="2">From the date of surgery up to 90 days post-surgery any new events which constitute post-operative complications (see protocol Appendix I) should be graded and captured on the post-operative complications CRF. Please refer to section 11.1.2 for timepoints.
All post-operative mortality events (deaths) should be reported as SAEs (90 days post-operative), regardless of cause.
Post-op complications do not need to be captured on the AE CRF.</td></tr>
</table>

APPENDIX O: Classification of Hepatic Dysfunction

Classification of Hepatic Dysfunction				
	Minimal	**Mild**	**Moderate**	**Severe**
AST	Greater than 3 x ULN	Normal	Normal	Normal
Bilirubin	Normal	Greater than 1 to 1.5 x ULN	Greater than 1.5 to 3 x ULN	Greater than 3 x ULN
Albumin	Normal	Normal	Normal	Normal
INR	Normal	Normal	Normal	Normal
			OR	**OR**
AST			Greater than 3 x ULN	Greater than 3 x ULN
Bilirubin			Greater than 1 to 1.5 x ULN	Greater than 1.5 to 3 x ULN
Albumin			Normal	Normal
INR			Normal	Normal
			OR	**OR**
AST			Normal	Normal
Bilirubin			Greater than 1 to 1.5 x ULN **and either**	Greater than 1.5 to 3 x ULN **and either**
Albumin			27 to 35 g/L **or**	Less than 28 g/L **or**
INR			1.4 to 1.7	Greater than 1.7
				OR
				Signs of liver decompensation

APPENDIX P: PROTOCOL AGREEMENT

I have read the Protocol:

Study Title:	Neo-AEGIS (NEO-adjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction
Study Number:	CTRIAL-IE [ICORG] 10-14
Version/date:	Version 12 / dated 27-Jul-2020

I agree to conduct the trial as detailed herein and in compliance with ICH Good Clinical Practice and all applicable regulatory requirements and to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions

_____

Principal Investigator (printed name)

_____ _____

Principal Investigator signature Date dd-MON-yyyy

_____

Investigational site or name of institution and location (printed)

Cancer Trials Ireland Country-Specific Appendix (CSA)
Version 6 27-Jul-2020

Study Title:	Neo-AEGIS (***NEO****adjuvant trial in* ***A****denocarcinoma of the o****E****sophagus and oesophago****G****astric junction* ***I****nternational* ***S****tudy*): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction
Cancer Trials Ireland Study Number:	CTRIAL-IE 10-14
Current Study Protocol Version:	Version 12, 27-Jul-2020 and subsequent approved versions
EudraCT No.:	2011-001858-28

IMPORTANT NOTE

This appendix is to be read in conjunction with the current approved version of the Cancer Trials Ireland 10-14 Neo-AEGIS study protocol. This Country Specific Appendix provides additional information/ instruction and/or replaces information/ instruction about trial conduct specifically in UK.

Sponsor	**Cancer Trials Ireland**, Innovation House, Old Finglas Road, Glasnevin, Dublin 11, Ireland
Chief Investigator	**Professor John V. Reynolds** Trinity Centre St. James's Hospital, Dublin 8 **Phone:** +353 1 896-2189 **Email:** reynoljv@tcd.ie
UK Trial Coordinating Centre	**Southampton Clinical Trials Unit** **Email**: neoaegis@soton.ac.uk
UK Coordinating Chief Investigators:	**Mr Shaun Preston** Royal Surrey County Hospital Oesophago-gastric Unit Egerton Road Guildford, GU2 7XX **Phone:** 01483 406688 **Email:** shaun.preston@nhs.net

Prof Tom Crosby
Velindre Cancer Centre
Cardiff, CF14 2TL
Phone: 02920316202
Email: tom.crosby@wales.nhs.uk

Cancer Trials Ireland Clinical Lead	**Prof Ray McDermott**, Cancer Trials Ireland
Cancer Trials Ireland Head of Clinical Operations	Padraig O'Grady Cancer Trials Ireland
Cancer Trials Ireland Project Manager	Anna Shevlin Cancer Trials Ireland

Protocol Section 1 Study Synopsis, page 14/15 and
Protocol Section 7.1 Inclusion Criteria 3, page 61,

Inclusion Criteria Number 3

"Endoscopic Ultrasound (EUS) in all patients unless luminal obstruction precludes sensitivity of the test." is not applicable in the UK. EUS is not mandatory and only required if deemed clinically indicated by the treating Investigator.

Rationale: EUS is being used less for routine staging in the UK and is not mandated for all cases by NICE. In addition, the scheduling of non-essential EUS is providing challenging with the ongoing COVID-19 pandemic. Although EUS now plays a lesser role in routine staging, it has an important role in treatment planning for a subgroup of patients. It is only required if deemed clinically indicated by the treating Investigator.

Protocol Section 1: Study Synopsis, Exclusion Criterion 13, page 15;
Protocol Section 7: Patient Selection Criteria, page 62

Exclusion Criteria Number 3

Co-enrolment into the Add-Aspirin trial is permitted for UK sites.

Protocol Section 2.5.2 Arm A – FLOT Chemotherapy Regimen, page 23

Per section 2.5.2, the drugs used in the FLOT regimen include 5-Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel. Leucovorin is available as calcium folinate or sodium folinate. The calcium folinate formulation at the protocol-specified dose of 200 mg/m² should be used for this trial. If the site pharmacy does not use calcium folinate as their standard of care form of Leucovorin in the FLOT regimen, the use of an alternative form of folinic acid will be allowed. This will be Sodiofolin (sodium folinate) at a flat dose of 350 mg.

If in doubt, please contact the Neo-AEGIS team at the SCTU for further discussions.

Protocol Section 4.3.2: Secondary End Points, page 29

Per section 4.3.2, one of the secondary end points for the trial is the surgical resection rate and this classification is determined by the 'distance of carcinoma to the nearest circumferential margin' measurement, as captured on the CRF. Although this data is required per the protocol, site 082 Newcastle will be exempt from reporting this data, as standardly the site dissects the lymph nodes post-operatively and it is therefore not possible to report the distance of carcinoma

to the nearest circumferential margin. These patients will be excluded from the final analysis in relation to this particular secondary end point.

Protocol Section 4.6: Drug Accountability Procedures, page 30

Capecitabine Prescriptions

The statement relating to Capecitabine prescriptions is only applicable in Ireland. In the UK, Capecitabine can be prescribed per local practice via the hospital pharmacy.

Protocol Section 6: Study Treatment Regimens, page 39

All chemotherapy agents should be administered according to the protocol. In situations where local practice differs from this, the chemotherapy agent can be administered according to local practice, as long as this is in line with the manufacturer's SmPC.

If in doubt, please contact the Neo-AEGIS team at the SCTU for further discussions.

Protocol Section 6.1.2.1: Arm A – Modified MAGIC Chemotherapy Regimen, page 39

5FU Administration

The 21-day infusion of 5FU may occur as a continuous infusion divided into 3 infusions, each lasting 7 days, as long as the total dose is maintained and infused over a 21-day period.

Protocol Section 6.2: Radiotherapy Trials Quality Assurance (RTTQA), page 43

The sentence "Patients treated with IMRT must be planned using 4-Dimensional CT (4DCT)" is not applicable in the UK. 4DCT is recommended but not mandatory.

Protocol Section 6.6: Dose Modifications and Delay Instructions, page 45

All chemotherapy agents should be administered according to the protocol. In situations where local practice differs from this, the chemotherapy agent can be administered according to local practice, as long as this is in line with the manufacturer's SmPC.

If in doubt, please contact the Neo-AEGIS team at the SCTU for further discussions.

Protocol Section 6.6.2: Dose Modifications for Arm B, page 58

Table 16 – CROSS Toxic Reactions and Prescribed Management, page60; Renal

If local practice is not to admit the patient overnight for an IV infusion, patients can be dose-adjusted according to local procedures.

Protocol Section 6.6.3: Radiation Toxicity, page 60

The sentence "4DCT planning and treatment should be used for all patients treated with IMRT" is not applicable in the UK. 4DCT is recommended but not mandatory.

Protocol Section 8.1: Patient Enrolment page, 62

When emailing a Patient Registration Form to Cancer Trials Ireland please ensure that you send to ALL of the following;

- neoaegis@soton.ac.uk
- patientregistrations@cancertrials.ie

When recording the DOB information on the patient registration form, the default number of **'01'** should be used for DD but the actual MM/YYYY completed. This same format should be used on all other e-CRF pages where a DOB field is required, including Serious Adverse Event reports.

Please note that any Patient Registration Forms sent to Cancer Trials Ireland and the SCTU which do not include the default DD of '01' will be rejected and you will be required to re-submit the form.

Patient Registration Forms emailed/faxed to Cancer Trials Ireland should never have any blacked out/covered/deleted sections and should always be a true reflection of the original.

Cancer Trials Ireland usually respond to patient registration emails within 1 hour. If you have not received a response after more than an hour please contact the SCTU on neoaegis@soton.ac.uk, who will be able to assist.

If you submit a Patient Registration Form towards the end of the day please note that it may not get processed until the following morning. If you require an **urgent** registration please contact the SCTU in advance who will notify Cancer Trials Ireland.

Protocol Section 9 Study Assessments and Procedures, page 64

Table 17: Study Assessments and Procedures: Screening – Registration, page 64

Screening Endoscopic Ultrasound (EUS) is not mandatory in UK and only required if deemed clinically indicated by the treating Investigator as outlined above.

Where it is not feasible for the Upper GI MDT discussion to confirm disease staging within 28 days prior to registration, sites are permitted to follow their own local standard of care regarding this timeline.

Table 21: Study Assessments and Procedures Post Surgery, page70

The follow up for UK patients will be as per protocol until the end of year 3.

Post disease progression or 3 years standard follow-up, patients will be followed up for survival every 6 months (+/- 6 week) until death or until the end of the trial, whichever occurs earlier.

Where site are able to determine 6 month (+/- 6 week) survival from a review of the notes, a separate survival call with the patient is not required. All survival data described in Protocol Section 9.8 Survival Follow-up should be documented.

Rationale: Routine in patient follow-up visits post 3 years are not in line with standard Follow-up practice in the UK.

Table 22: Disease Assessments (Both treatment arms), footnote (a), page 71

Follow-up OGDs at 1 year post-registration and 2 years post-registration need only be carried out if clinically indicated. If these procedures are clinically indicated, this must be documented in the source data by a study investigator.

The follow-up OGD at the 3 years post-registration time point remains mandatory in the UK.

Please note that the follow-up CT/CT-PET scans remain mandatory in the UK at all time points (i.e. 1 year post-registration, 2 years post-registration and 3 years post-registration).

Protocol Section 9.2 Screening Visit Assessments (page 73/74)

Screening Endoscopic Ultrasound (EUS)

A screening EUS is not mandatory in the UK and only required if deemed clinically indicated by the treating Investigator as outlined above.

Multi-Disciplinary Team Meeting

Where it is not feasible for the Upper GI MDT discussion to confirm disease staging within 28 days prior to registration, sites are permitted to follow their own local standard of care regarding this timeline.

Protocol Section 9.5: Assessments required within 8 weeks post last dose of neoadjuvant treatment (for both treatment arms), page 75

The restaging CT or CT-PET scan of the thorax, abdomen and neck (as per institutional standard practice) and restaging OGD can be carried out per local standard of care (e.g. immediately after neoadjuvant treatment if mandated) as long as they occur within 8 weeks post last dose of neoadjuvant treatment, in line with the protocol.

Protocol Section 9.7: Assessments required post surgery (for both arms), page 76;
Protocol Section 9.8 Survival Follow-up, page 76

The follow up for UK patients will be as per protocol until the end of year 3.

Post disease progression or 3 years standard follow-up, patients will be followed up for survival every 6 months (+/- 6 week) until death or until the end of the trial, whichever occurs earlier.

Where site are able to determine 6 month (+/- 6 week) survival from a review of the notes, a separate survival call with the patient is not required. All survival data described in Protocol Section 9.8 Survival Follow-up should be documented.

OCCAMS Consortium

CRUK have funded whole genome sequencing of gastro-oesophageal adenocarcinoma as part of the International Cancer Genome Consortium. This is resulting in unprecedented detailed

characterisation of the mutations in cancer which will lead to new clinical trials using targeted agents which could improve clinical outcomes. The OCCAMS study is acting as the translational aspect of the Neo-AEGIS trial in the UK, and it is therefore imperative that we take full advantage of this and obtain sequencing data from as many Neo-AEGIS patients as possible.

For information about joining the OCCAMS Consortium, please contact neoaegis@soton.ac.uk.

This Country Specific Appendix is approved by the following:

Prof. John Reynolds		16-Oct-2020
Chief Investigator (Print Name)	Signature	Date (dd-MON-yyyy)
Dr Tom Crosby		20-Oct-2020
National Coordinating Investigator (UK)	Signature	Date (dd-MON-yyyy)
Imelda Parker	Imelda Parker Digitally signed by Imelda Parker Date: 2020.10.20 11:34:20 +01'00'	
Group Statistician (Print Name)	Signature	Date (dd-MON-yyyy)
Padraig O'Grady	Padraig O'Grady Digitally signed by Padraig O'Grady DN: cn=Padraig O'Grady, o=Cancer Trials Ireland, ou=GCO-CTI, email=padraig.ogrady@cancertrials.ie, c=IE Date: 2020.10.16 15:43:37 +01'00'	
Head of Clinical Operations and Clinical Programs	Signature	Date (dd-MON-yyyy)

The UK Version 6 Country Specific Appendix is authorised by the following:

Prof. Ray McDermott		26-Oct-2020
Clinical Lead	Signature	Date (dd-MON-yyyy)

This Country Specific Appendix is accepted by the following:

I will conduct the study in accordance with this Country Specific Appendix in conjunction with the current approved version of the study protocol.

Principal Investigator (Print Name)	Signature	Date (dd-MON-yyyy)

Protocol Country Specific Appendix

Version 3 / 28-Oct-2020

Study Title:	**Neo-AEGIS** (NEO-adjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction
Cancer Trials Ireland Study Number:	CTRIAL-IE 10-14
Current Study Protocol	Version 12 27-Jul-2020
EudraCT No.:	2011-001858-28

IMPORTANT NOTE

This appendix is to be read in conjunction with the current approved version of the Neo-Aegis 10-14 study protocol. This Country Specific Appendix provides additional information/ instruction and/or replaces information/ instruction about trial conduct specifically in Karolinska Institutet and Karolinska University Hospital, Sweden, managed by Karolinska University Hospital

Sponsor:	Cancer Trials Ireland, Innovation House, Old Finglas Road, Glasnevin, Dublin 11, Ireland
Country Specific Coordinating Centre	Clinical Trials Office, Centre for Clinical Cancer Studies, Karolinska University Hospital, Stockholm, Sweden
Chief Investigator	Professor John Reynolds, St James Hospital
National Coordinating Investigator Sweden	Professor Magnus Nilsson, Karolinska Institutet and Karolinska University Hospital

Cancer Trials Ireland

Clinical Lead	Professor Ray McDermott, Tallaght University Hospital
Head of Clinical Operations	Dr Padraig O'Grady
Project Manager	Anna Shevlin
Group Statistician	Dr Imelda Parker

Amendment to;
Protocol Section 1 Study Synopsis (page 14/15) and
Protocol Section 7.1 Inclusion Criteria (page 61),

Inclusion Criteria Number 3

"Endoscopic Ultrasound (EUS) in all patients unless luminal obstruction precludes sensitivity of the test." is not applicable in Sweden. EUS is not mandatory and only required if deemed clinically indicated by the treating Investigator.

Rationale: Screening EUSs are not carried out as standard for all patients in Sweden. Several publications in the last 5-10 years have shown that with the development of better CT/PET-CT technology, EUS does not influence patient management very often, and is consequently not cost efficient. The Karolinska and many leading centres internationally have moved from routine use, to a more tailored use, i.e. only for specific indications such as suspected T4b or biopsy of suspected extra-regional lymph node metastases. In addition, for airway overgrowth, in Sweden it is generally preferred to use EBUS instead of EUS.

Inclusion Criteria Number 10

The following sentence in the protocol

*"***Inclusion Criteria Number 10:** *Adequate cardiac function. For all patients, an ejection fraction of > 50% is required. If patients have a known cardiac history (e.g. known ischemic disease, cardiomyopathy) an ejection fraction > 50% and cardiac clearance by a consultant cardiologist for major surgery and cancer therapies is required."* is not applicable in Sweden. An assessment of ejection fraction by ECHO or MUGA is not mandatory and only required if deemed clinically indicated (e.g. cardiac history and/or cardiac symptoms) by the treating Investigator.

Is replaced with

"In the opinion of the treating Investigator the patient has adequate cardiac function for major surgery and cancer therapies. For patients with a known cardiac history (e.g. known ischemic disease, cardiomyopathy) or cardiac symptoms *an ejection fraction > 50% is required."*

Rationale: The Neo-Aegis trials compares two standard of care regimes and as such the treatment and assessments all patients undergo should be in line with local standard of care. In Sweden screening MUGA/ECHO is not generally a routine and is only performed if it is indicated e.g. cardiac history and/or cardiac symptoms. The reason is that there is no evidence that it adds any value in otherwise fit, relatively young patients without any history of cardiac disease.

Inclusion Criteria Number 16

The following sentence in the protocol

"Inclusion Criteria Number *16:* Women of child-bearing potential and male subjects must agree to use an effective barrier method of contraception for up to 6 months following discontinuation of therapy. Effective contraception is defined as any medically recommended (or combination of methods) as per standard of care."

Is replaced with

"Inclusion Criteria Number 16: *Women of childbearing potential (WOCBP) and sexually active males must agree to use highly effective contraceptive measures. This applies from starting treatment until at least 6 months after the last study drug administration. The investigator or a designated associate is required to advise the patient how to achieve an adequate birth control. Highly effective contraception is defined in the study as methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include:*

i. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable and implantable).
iii. Intrauterine device (IUD).
iv. Intrauterine hormone-releasing system (IUS).
v. Bilateral tubal occlusion.
vi. Successfully vasectomised partner.
vii. Sexual abstinence."

Amendment to;
Protocol Section 6.6.1.1 ECX Regimens dose modification, delay and stopping instructions (Page 47) and
Protocol Section 6.6.1.2 ECF Regimens dose modification, delay and stopping instructions (Page 50)

The following sentence in the protocol is not applicable as Epirubicin will not be used in Sweden. Sweden will only use the FLOT regimen for the perioperative chemotherapy arm

"Precautions Point 4.
Cardiac toxicity: *Clinical cardiac assessment is required prior to epirubicin if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO)."*

And

The following sentence in the protocol is not applicable as Cisplatin will not be used in Sweden. Sweden will only use the FLOT regimen for the perioperative chemotherapy arm

"Ototoxicity / Hearing impairment:
For patients with hearing impaired adverse event ≥ grade 1 and/or tinnitus or other 'ear and labyrinth disorder' ≥ grade 2, cisplatin may be switched to oxaliplatin following discussion with the sponsor/CI (on a per patient basis)."

Amendment to; Section 9 Study Assessments and Procedures- Table 17 (page 64)

Screening Endoscopic Ultrasound (EUS) and ECHO/MUGA are not mandatory in Sweden and only required if deemed clinically indicated by the treating Investigator as outlined above.

Hearing Assessments are not applicable in Sweden as Cisplatin will not be used.

Table 18: Study Assessments and Procedures for Arm A: MAGIC (neoadjuvant treatment pre-surgery)

Hearing Assessments are not applicable in Sweden as Cisplatin will not be used.

Amendment to; Section 9.2 Screening Visit Assessments (page 73/74)

Hearing Assessment

The following sentence in section 9.2 of the protocol

"Point 2: Clinical history and physical examination, including ECOG performance status, ASA grading (Appendix D), weight and hearing assessment.

Is replaced with

"Point 2: Clinical history and physical examination, including ECOG performance status, ASA grading (Appendix D) and weight"

Endoscopic Ultrasound (EUS)

The following sentence in section 9.2 of the protocol

*"Point 4: The following assessments and investigations must be performed within 28 calendar days prior registration, unless otherwise specified below: Endoscopic Ultrasound** ***This procedure does not need to be repeated if done 42 calendar days prior to registration. Please refer to Table 17 letter (d), for guidance on tests older than 42 calendar days and if not feasible to repeat. "***

Is replaced with

"A screening EUS is not mandatory in Sweden and only required if deemed clinically indicated by the treating Investigator. "

Screening ECHO or MUGA

The following sentence in section 9.2 of the protocol

"Point 15: The following assessments and investigations must be performed within 28 calendar days prior registration, unless otherwise specified below: "Assessment of left ventricular ejection fraction (LVEF) by either multigated acquisition scan (MUGA) or echocardiogram (ECHO). Ejection fractions ≤50% and the absence of any significant wall motion abnormality should be documented. Patients must have adequate cardiac function to participate in this trial. Patients with known cardiac history should have a left ventricular ejection fraction > 50% (as determined by MUGA scan or ECHO) prior to enrolment in this trial and cardiac clearance by a consultant cardiologist for major surgery and cancer therapies is required. ***This procedure does not need to be repeated if completed within 42 calendar days prior to registration. "***

Is replaced with

"An assessment of ejection fraction by ECHO or MUGA at screening is not mandatory in Sweden and only required if deemed clinically indicated (e.g. cardiac history and/or cardiac symptoms) by the treating Investigator. For patients with a known cardiac history (e.g. known ischemic disease, cardiomyopathy) or cardiac symptoms *an ejection fraction > 50% is required to participate in this trial."*

Amendment to;
Protocol Section 9 Study Assessments and Procedures,
Table 18 Study Assessments and Procedures for Arm A: MAGIC (neoadjuvant treatment pre-surgery) (page 66/67),
Table 19: Study Assessments and Procedures for Arm A: FLOT (neoadjuvant treatment pre-surgery) (page 67/68),
Table 20: Study Assessments and Procedures for Arm B (Page 69/70).

The following sentence in table 18, 19, 20 of the protocol

"Point d and e: Restaging PET-CT or CT and OGD should occur within 4-8 weeks of finishing treatment. Countries where local standard of care mandates this to happen immediately after neoadjuvant treatment, is also acceptable"

Is replaced with

"Point d and e: Restaging PET-CT or CT should occur within 4-8 weeks of finishing treatment. Countries where local standard of care mandates this to happen immediately after neoadjuvant treatment, is also acceptable. Restaging OGD should occur in line with local standard of care timelines; immediately after neoadjuvant treatment, within 4-8 weeks of finishing treatment or during surgery are acceptable."

Rationale: Re-staging OGD not standardly done pre-surgery in Sweden. It is standardly done during surgery. Routinely performing restaging OGD before surgery does not add any important information that cannot be gathered if the OGD is performed during surgery, which is routine in Sweden. Restaging OGD is carried out only if clinically indicated for example, done pre-surgery if any issues of respectability that can be addressed by OGD. Internationally practice varies and routine restaging OGD before surgery is not global standard of practice.

Amendment to;
Protocol Section 9.5 Assessments required within 8 weeks post last dose of neoadjuvant treatment (for both treatment arms) (Page 75).

The following sentence in the protocol

"Protocol Section 9.5 Assessments required within 8 weeks post last dose of neoadjuvant treatment (for both treatment arms).
Please refer to group specific appendix if local standard of care differs from these timelines.
1. A restaging CT or CT-PET scan of the thorax, abdomen and neck (as per institutional standard practice) will be performed after completion of trial treatment
A restaging OGD to assess endoscopic response"

Is replaced with

"Protocol Section 9.5 Assessments required within 8 weeks post last dose of neoadjuvant treatment (for both treatment arms).
Please refer to group specific appendix if local standard of care differs from these timelines.
1. A restaging CT or CT-PET scan of the thorax, abdomen and neck (as per institutional standard practice) will be performed after completion of trial treatment.
A restaging OGD to assess endoscopic response should occur in line with local standard of care timelines; immediately after neoadjuvant treatment, within 4-8 weeks of finishing treatment or during surgery are acceptable."

Amendment to protocol Section 12.9.3 Record Retention (Page 90),

The following sentence in the protocol

"An investigator site file will be provided by Cancer Trials Ireland for all required trial documents. The investigator will maintain all trial records according to ICH/GCP and applicable regulatory requirement(s). The Sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion. However, this will extend to 25 years due to changes in the law which will apply from 2021. Cancer Trials Ireland as Sponsor will notify investigators when they are no longer required to maintain the files. If the investigator withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept the responsibility and this must be documented in writing to Cancer Trials Ireland."

Is replaced with

"An investigator site file will be provided by Cancer Trials Ireland for all required trial documents. The investigator will maintain all trial records according to ICH/GCP and applicable regulatory requirement(s). The Sponsor and the investigator shall retain the essential documents relating to the clinical trial for at least five years after its completion, ***with the exception of Sweden. In accordance with*** **Swedish legislation** ***the Swedish investigator(s) shall retain the essential documents relating to the clinical trial for at least ten years after its completion. In Ireland, this will extend to 25 years due to changes in the law which will apply from 2021.*** *Cancer Trials Ireland as Sponsor will notify investigators when they are no longer required to maintain the files. If the investigator withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept the responsibility and this must be documented in writing to Cancer Trials Ireland."*

End of Trial

All patients will be followed up until death or until the last patient has completed 18 months follow-up, whichever occurs earlier. The End of Trial and Last Patient Last Visit (LPLV) date is defined as the date the last patient has been followed for 18 months from randomisation.

- Estimated Last Patient Randomised: 31-Sep-2021
- Estimated Last Patient Last Visit: 30-Mar-2023

Risk-benefit considerations

Study Level Assessment

This is a Phase III open-labelled, randomised controlled trial. All investigational agents are licensed and commercially available. The trial compares two regimens (FLOT or CROSS) of which both are considered standard of care for patients with adenocarcinoma in the oesophagus or the gastro-oesophageal junction in Sweden.

All IMP are well established products with well documented safety profiles. The local Investigators are experienced in their use. In addition, an independent Data Safety Monitoring Board (DSMB) is in place to monitor safety and efficacy data.

All assessments and procedures are in line with International standard of care.

There are no extra medical risks to the patients from participation in the trial and the benefit-risk balance should, if anything, be in favour of being treated within the trial, as follow-up and adverse event assessment are likely to be even more meticulous within the trial, compared to in ordinary clinical practice.

The trial is considered to be a low risk study as it is in line with standard of care, has a large (540 patient) phase III randomised unblinded design, is low in complexity and the safety profile of the regimens are well known. The trial has a positive benefit - risk assessment.

COVID 19 Assessment

Even in the presence of the covid-19 pandemic patients with adenocarcinoma in the oesophagus or the gastro-oesophageal junction are offered one of the two treatments regimens, and participation in the trial brings no extra risk.

Possible perceived risks include potential patient exposure to COVID-19 by attendance at the clinic and late/missed assessments due to patient non-attendance. However, this is an equally existing risk in patients treated outside the trial, and is not in any way more problematic within the trial. The trial site continues to take measures to reduce the potential exposure of their at-risk patient population to COVID-19.

A possible perceived risk is late/missed assessments and delayed data entry due to potential resource issues at the site due to COVID-19 capacity issues. No such resource issues exist at the site at present.

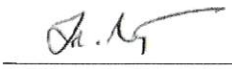
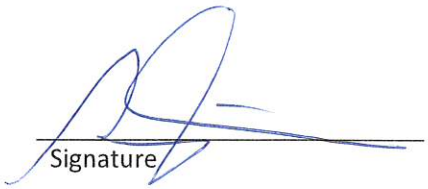
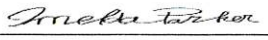
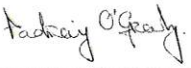
A benefit from participation is the close monitoring associated with a clinical trial.

As detailed in the Clinical Trial Application, it is anticipated the earliest the study will open in Sweden is Sept/Oct 2020 when the COVID-19 pandemic is expected to be under further

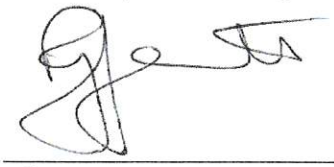
control. A further risk assessment will be conducted by the Sponsor before initiated and activating the site to ensure the benefit risk assessment remains unchanged. Arrangements must be in place for the monitor to have access to site for initiation and monitoring.

As always, the decision to recruit an individual patient to a clinical trial is taken by a Consultant / Investigator after a careful consideration of the risks and benefits of participation.

This Country Specific Appendix is approved by the following:

Professor John Reynolds		02-Nov-2020
Chief Investigator Professor John Reynolds	Signature	Date (dd-MON-yyyy)
Professor Magnus Nilsson		04 Nov-2020
National Coordinating Investigator Sweden Professor Magnus Nilsson	Signature	Date (dd-MON-yyyy)
Dr Imelda Parker		02-Nov-2020
Group Statistician Dr Imelda Parker	Signature	Date (dd-MON-yyyy)
Padraig O'Grady		02-Nov-2020
Head of Clinical Operations Padraig O'Grady	Signature	Date (dd-MON-yyyy)

The Country Specific Appendix is authorised by the following:

Professor Ray McDermott		04-Nov-2020
Clinical Lead Professor Ray McDermott	Signature	Date (dd-MON-yyyy)

This Country Specific Appendix is accepted by the following:

I will conduct the study in accordance with this Country Specific Appendix in conjunction with the current approved version of the study protocol.

Principal Investigator (Print Name)	Signature	Date (dd-MON-yyyy)

Rigshospitalet

cancer trials ireland
Together, we're finding answers to cancer.

Cancer Trials Ireland Group-Specific Appendix (GSA)

Version 4.0 28-Oct-2020

Study Title:	Neo-AEGIS (***NEO****adjuvant trial in* ***A****denocarcinoma of the o****E****sophagus and oesophago****G****astric junction* ***I****nternational* ***S****tudy*): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction
Cancer Trials Ireland Study Number:	CTRIAL-IE 10-14
Current Study Protocol Version:	Version 12, 27-Jul-2020 and subsequent approved versions
EudraCT No.:	2011-001858-28

IMPORTANT NOTE

This appendix is to be read in conjunction with the current approved version of the Cancer Trials Ireland 10-14 Neo-AEGIS study protocol. This Country Specific Appendix provides additional information/ instruction and/or replaces information/ instruction about trial conduct specifically in Denmark.

Sponsor	**Cancer Trials Ireland,** Innovation House, Old Finglas Road, Glasnevin, Dublin 11, Ireland
Chief Investigator	**Professor John V. Reynolds** Trinity Centre St. James's Hospital, Dublin 8 **Phone:** +353 1 896-2189 **Email:** reynoljv@tcd.ie
Coordinating Group	**Rigshospitalet,** Blegdamsvej 9,

	2100 Copenhagen, Denmark
National Coordinating Investigator	**Dr Lene Bæksgaard**, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
Cancer Trials Ireland Clinical Lead	**Prof Ray McDermott**, Cancer Trials Ireland
Cancer Trials Ireland Head of Clinical Operations and Clinical Programs	Padraig O' Grady Cancer Trials Ireland
Cancer Trials Ireland Project Manager	Anna Shevlin Cancer Trials Ireland

1. Supplement to Protocol Section 1 Study Synopsis, Section 7.1 Inclusion Criteria point 3 and Section 9 Study Assessments and Procedures, Table 17

The above sections of the CTRIAL-IE (ICORG) 10-14 NeoAEGIS Protocol which reference the requirement to perform an Endoscopic Ultrasound will not be applicable to Denmark based on the following rationale:

According to Danish national guidelines, an Endoscopic Ultrasound (EUS) should only be performed in pre-therapeutic staging, A) if there is a possibility for changing the treatment decision, i.e. in the case of suspected T1N0 tumors (those patients should proceed directly to surgery without neoadjuvant treatment) or B) in selected cases of suspected T4NX-tumors (with the suspicion of non-resectability).

For all other patients with oesophageal cancer, EUS does not influence the treatment decision because the patients will receive neoadjuvant therapy; therefore this procedure will not performed routinely as part of the staging procedures in Denmark because it would not be covered by the Danish Health System.

The gastroscopy, as part of the standard staging procedures will, be performed before inclusion into the study according to protocol as well a CT-PET scan and laparoscopy.

Only patients which are eligible according to the staging criteria listed in the protocol will be enrolled in this study in Denmark.

2. Supplement to Protocol Section 2.5.3, Arm B – Cross Protocol: Chemotherapy and Radiotherapy Regimen

In Denmark, the ASCO Guidelines on antiemetics will be followed, with a minor modification. Please see below dose and schedule which will be followed:

Cycle 1:

Cetirizine 10 mg day 1 taken orally

Ranitidine 50 mg day 1 given intravenously

MethylPrednisolone 40 mg day 1 given intravenously

Prednisolone 50 mg day 2+3 taken orally

Ondansetron 16 mg day 1 taken orally

Cycle 2:

Cetirizine 10 mg day 1 taken orally

Ranitidine 50 mg day 1 given intravenously

MethylPrednisolone 40 mg day 1 given intravenously

Prednisolone 50 mg day 2+3 taken orally

Ondansetron 16 mg day 1 taken orally

Cycle 3:

Cetirizine 10 mg day 1 taken orally

Ranitidine 50 mg day 1 given intravenously

MethylPrednisolone 20 mg day 1 given intravenously

Prednisolone 50 mg day 2+3 taken orally

Ondansetron 16 mg day 1 taken orally

Cycle 4:

Cetirizine 10 mg day 1 taken orally

Ranitidine 50 mg day 1 given intravenously

MethylPrednisolone 20 mg day 1 given intravenously

Prednisolone 50 mg day 2+3 taken orally

Ondansetron 16 mg day 1 taken orally

Cycle 5:

t. Cetirizin 10 mg day 1

t. Ranitidine 150 mg day 1

t. Prednisolone 50 mg day 1+2+3

t. Ondansetron 16 mg day 1

3. Supplement to Protocol Section 9.7, Assessments required post-surgery (for both treatment arms) – Follow Up Visits

This supplement refers to point 3 which states: *Follow-up visits at the trial centre will occur at 3 months, 6 months, 9 months and 12 months for the 1st year and 6 monthly thereafter for a maximum of 5 years or until progression of disease is documented or death or until the last patient has completed 18 months follow up, whichever occurs earlier.*
As per standard of care at Danish site 101, patients remain in Standard Follow Up for a maximum of 3 years. After 3 years of Standard Follow Up patients proceed to Survival Follow Up Visits. This supplement to *Protocol Version 12, dated 27-Jul-2020* and subsequent approved versions is in keeping

with Danish Patient Information Leaflet *Deltagerinformation og samtykkeerklæring Version 8 3.Juni 2019,* which details that patients remain in Standard Follow Up until their 3 year control.

This Country Specific Appendix is approved by the following:

Prof John Reynolds		30-Oct-2020
Chief Investigator (Print Name)	Signature	Date (dd-MON-yyyy)
Dr Lene Bæksgaard		24 Nov 2020
National Coordinating Investigator (Denmark) (Print Name)	Signature	Date (dd-MON-yyyy)
Imelda Parker	Imelda Parker Digitally signed by Imelda Parker Date: 2020.10.29 14:43:23 Z	
Group Statistician (Print Name)	Signature	Date (dd-MON-yyyy)
Padraig O'Grady		02-Nov-2020
Head of Clinical Operations and Clinical Programs (Print Name)	Signature	Date (dd-MON-yyyy)

The DK Version 4 Group Specific Appendix is authorised by the following:

Prof. Ray McDermott		30-Oct-2020
Clinical Lead (Print Name)	Signature	Date (dd-MON-yyyy)

This Country Specific Appendix is accepted by the following:

I will conduct the study in accordance with this Country Specific Appendix in conjunction with the current approved version of the study protocol.

Lene Bæksgaard		24 Nov 2020
Principal Investigator (Print Name)	Signature	Date (dd-MON-yyyy)

Protocol Country Specific Appendix

Version 6.0/ 04-Nov-2020

Study Title:	**Neo-AEGIS** (NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study): Randomized Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction.
Cancer Trials Ireland Study Number:	CTRIAL-IE 10-14
Current Study Protocol:	Version 12, 27-Jul-2020 (and subsequent approved versions)
EudraCT No.:	2011-001858-28
Réf. Promoteur :	2014_42

IMPORTANT NOTE

This appendix is to be read in conjunction with the current approved version of the CTRIAL-IE 10-14 Neo-AEGIS study protocol. This Country Specific Appendix provides additional information/ instruction and/or replaces information/ instruction about trial conduct specifically in France, site(s) managed by CHU de Lille.

Sponsor	Cancer Trials Ireland, Innovation House, Old Finglas Road, Glasnevin, Dublin 11, Ireland
Chief Investigator	Professor John Reynolds, St. James's Hospital, Dublin 8
Country Specific Coordinating Group	Centre Hospitalier Universitaire de Lille, 2, avenue Oscar Lambret, 59037 Lille Cedex, France
National Coordinating Investigator France	Professor Guillaume Piessen, Department of General and Digestive surgery, Lille University

Cancer Trials Ireland

Clinical Lead	Prof. Ray McDermott, Tallaght University Hospital
Chief Executive Officer	Eibhlín Mulroe
Project Manager	Anna Shevlin
Group Statistician	Dr Imelda Parker

In order to comply with French regulation, the following underlined paragraph had been added:

Section 2.5.1 (page 22)

- ✓ The 21-day infusion of 5FU may occur as a continuous infusion divided into 3 infusions, each lasting 7 days, as long as the total dose is maintained and infused over a 21-day period.

Section 2.6.1.1 (page 25)

"Epirubicin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of Epirubicin.

Yellow fever vaccine is contraindicated in patients receiving treatment with Epirubicin.

As with other chemotherapy agents which alter DNA, myelodysplasic and acute myeloid leukemia syndroms have been observed after combined treatments including Epirubicin. Some secondary leukemia induced by chemotherapy agents can be cured provided that an early and adapted care is performed. Consequently, hematologic monitoring has to be performed for each patient treated with Epirubicin".

Section 2.6.7 (page 27)

"Oxaliplatin should be used in specialized departments of oncology and administered under the supervision of an experienced oncologist.

A special care has to be performed among patients with known medical history of allergic reactions to other products containing platin. If anaphylactic reactions occur, the infusion of Oxaliplatin should be discontinued immediately and appropriate symptomatic treatments should be started. Resuming of Oxaliplatin treatment is contra-indicated. Crossed reactions, sometimes leading to death, have been reported with all products containing platin."

Section 4.2.1 (page 28) – this was also added to the protocol synopsis adapted for use in France):

It is anticipated that 540 patients will be accrued to this study at participating study sites located in Ireland, United Kingdom, Denmark and France. *Approximately 60 patients are expected to be included in France.*

Section 6.2 (Page 43): Radiotherapy Trials Quality Assurance (RTTQA)

The sentence "*Patients treated with IMRT must be planned using 4-Dimensional CT (4DCT)*" is not applicable in France. 4DCT is recommended but not mandatory.

Section 6.6.1 (page 45, page 47)

"**4.** Cardiac Toxicity: Clinical cardiac assessment is required prior to Epirubicin if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO). *If the ventricular ejection fraction is measured below 50%, the treatment with Epirubicin will be discontinued. An echocardiography will be performed after the end of treatment with Epirubicin"*.

Section 6.6.1.3 (page 55)

"*11. *Cardiac toxicity: According to data related to cardiotoxicity of Oxaliplatin treatment (risk of corrected QT interval (QTc) prolongation and torsade de pointes), an ECG will be performed before and after each intravenous infusion of Oxaliplatin. In case of QTc (using Bazett's (QTcB) or Fridericia's (QTcF) formula) prolongation longer than 500 msec, the treatment with Oxaliplatin will be discontinued and a close and adapted ECG monitoring (continuously) in the hospital environment will be performed until cardiologist's advice.*

Medicines known to increase the QTc interval have to be used with caution. A list of those medicines is available on the following link: http://www.crediblemeds.org".

Section 6.6.1.4 (page 55)

"*In case of infection, fever or digestive disorders evocative of enterocolitis, a full blood count is recommended*".

Section 7.1. Inclusion criteria (page 61, Synopsis pages 15-16)

"**12.** Adequate bone marrow function: *absolute neutrophil count (ANC) > 2.0 X 10^9/l* ~~>1.5x109/l~~; white blood cell count > 3x10^9/l; platelets > 100x10^9/l; hemoglobin (Hb) > 9g/dl (can be post-transfusion)".

"**18.** *Patients covered by a Health Insurance System*".

Section 7.2. Exclusion criteria (pages 61-62, Synopsis page 16):

"**1.** Tumours of squamous histology *or patients with haemorrhagic tumours"*.

"**4.** Any prior chemotherapy for gastrointestinal cancer *or patients already treated with Epirubicin or other anthracyclines or anthracenediones for any cancer".*

"**6.** Patients who are unfit for surgery or cancer treatments based on cardiac disease. *QTc (using Bazett's (QTcB) or Fridericia's (QTcF) formula) interval longer than 450 msec for men and longer than 470 msec for women on the ECG performed at screening*."

"**16.** *At screening, patients with hypokalemia, hypomagnesemia or hypocalcemia*" .

"**17.** *Patients in emergency situations".*

"**18.** *Patients kept in detention."*

Section 9 Study Assessments and Procedures / Table 18: Study Assessments and Procedures for Arm A: MAGIC (neoadjuvant treatment pre-surgery) [page 66] / Table 19: Study Assessments and Procedures for Arm A: FLOT (neoadjuvant treatment pre-surgery) [page 67] / Table 20: Study Assessments and Procedures for Arm B [page 69]

In accordance with standard of care in France:

- In case of disease progression during or after neo-adjuvant treatment and prior to surgery the post re-staging upper GI Multi-Disciplinary Team (MDT) discussion will take place post neo-adjuvant treatment and prior to surgery.
- In case of no disease progression after completion of neoadjuvant treatment the post re-staging upper GI MDT discussion will take place post-surgery.

Section 9.4, page 75

"*Female patients of childbearing potential should have pregnancy excluded by urine or serum beta-HCG testing every month during the whole study treatment (for both treatment arms)*" .

The following has been added to the protocol synopsis adapted for use in France:

Assessment of benefits and risks related to the research:

Benefits. Apart from the expected clinical benefit, no direct benefit is expected for the patient compared to current medical care. Nevertheless, the results of this study will allow a more adapted medical care for patients suffering with adenocarcinoma of the oesophagus or oesophago-gastric junction.

Risks. Participation in this study does not expose the patient to additional risks compared to current medical care. There are no specific side effects linked to this study apart from the potential usual side effects linked to the treatments used (chemotherapy and radiotherapy), which will be detailed to patients by investigators. The surgical approach used in this study will be the one usually practiced. Participating in the study does not modify the scheduled surgical approach.

This Country Specific Appendix is approved by the following:

Prof John Reynolds		
Chief Investigator (Print Name)	Signature	Date (dd-MON-yyyy)
Prof Guillaume Piessen		
National Coordinating Investigator, France (Print Name)	Signature	Date (dd-MON-yyyy)
Imelda Parker		
Group Statistician (Print Name)	Signature	Date (dd-MON-yyyy)
Eibhlín Mulroe		
Chief Executive Officer (Print Name)	Signature	Date (dd-MON-yyyy)

This Country Specific Appendix is authorised by the following:

Prof. Ray McDermott		
Clinical Lead (Print Name)	Signature	Date (dd-MON-yyyy)

This Country Specific Appendix is accepted by the following:

I will conduct the study in accordance with this Country Specific Appendix in conjunction with the current approved version of the study protocol.

Principal Investigator (Print Name)	Signature	Date (dd-MON-yyyy)