PROTIEUS

A Randomised Phase 2 Trial Comparing Proton versus Photon Based Neoadjuvant Chemoradiation, followed by standard therapy in Oesophageal Cancer

Trial Sponsor:	University College London
Trial Sponsor reference:	UCL156414
Trial funder:	Cancer Research UK
Funder reference:	CRUK/22/011
ISRCTN no:	50098578
IRAS ID:	329646
Protocol version no:	5.0
Protocol version date:	8th January 2026

CANCER RESEARCH UK | Cancer Trials Centre | UCL | RTTQA Radiotherapy Trials Quality Assurance

Protocol version 5.0 (8th January 2026), Authorisation signatures:

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Please note: This trial protocol must not be applied to patients outside the PROTIEUS trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

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ABBREVIATIONS

AE	Adverse Event
AEIP	Adverse event of importance for PROTIEUS
ALT	Alanine Transaminase
AR	Adverse Reaction
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
cfDNA	Cell-free DNA
CI	Chief Investigator
CMR	Cardiovascular Magnetic Resonance
CPET/CPEX	Cardiopulmonary exercise testing
CR	Complete Response
CRF	Case Report Form
CRT	Chemoradiotherapy
CSRI	Client Service Receipt Inventory
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volumes
DFS	Disease-Free Survival
DNA	Deoxyribonucleic acid
DPYD	Dihydropyrimidine dehydrogenase
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case report Form
ECX	Epirubicin, Cisplatin, Capecitabine
EDTA	Ethylene Diamine Tetra Acetate
EFS	Event Free Survival
EUS	Endoscopic Ultrasound
FBC	Full Blood Count
FFPE	Formalin fixed paraffin embedded
FLOT	Fluorouracil, leucovorin, oxaliplatin and docetaxel chemotherapy combination
GDPR	General Data Protection Regulation (i.e. UK GDPR (as defined in section 3(10) (as supplemented by section 205(4)) of the Data Protection Act 2018)); and (to the extent that it applies) the General Data Protection Regulation (EU)2016/679 (EU GDPR)
GOJ	Gastroesophageal junction
GTV	Gross tumour volume
Gy	Gray
HRA	Health Research Authority
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiotherapy
IO	Immunotherapy
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number

LDH	Lactate Dehydrogenase
IV	Intravenous
MDT	Multi-Disciplinary Team
MRI	Magnetic Resonance Image
MUGA	Multi Gated Acquisition scan
NAT	Neoadjuvant Therapy
neoCRT	Neoadjuvant chemoradiotherapy
NHS	National Health Service
OAC	Oesophageal adenocarcinoma
OC	OpenClinica (Database)
OEC	Oesophageal cancer
OS	Overall Survival
OSCC	Oesophageal Squamous Cell Carcinoma
PBT	Proton Beam Therapy
pCR	Pathologic Complete Response
PD	Progressive Disease
PEG	Percutaneous Endoscopic Gastrostomy
PFS	Progression Free Survival
PI	Principal Investigator
POC	Post-operative Complications
PR	Partial Response
PTV	Planning Target Volume
QALY	Quality-adjusted life-year
QoL	Quality of Life
RBE	Relative Biological Effectiveness
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RIC	Radiation-induced cardiotoxicity
RIG	Radiologically Inserted Gastrostomy
RNA	Ribonucleic Acid
RT	Radiotherapy
RTQA	Radiotherapy Quality Assurance
RTTQA	Radiotherapy Trials Quality Assurance
R0	Complete Resection
R1	Incomplete Resection
SACT	Systemic Anticancer Therapy
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
SPC	Summary of Product Characteristics
TMF	Trial Master File
TMG	Trial Management Group
TRG	Tumour Regression Grade
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
UIP	Usual Interstitial Pneumonia
UK	United Kingdom
VMAT	Volumetric Arc Radiotherapy

1. PROTOCOL SUMMARY

1.1 Summary of Trial Design

Title:	A Randomised Phase 2 Trial Comparing Proton versus Photon Based Neoadjuvant Chemoradiation, followed by standard therapy, in Oesophageal Cancer
Short Title/acronym:	PROTIEUS
Sponsor name & reference:	University College London (ref: 156414)
Funder name & reference:	Cancer Research UK (ref: CRUK/22/011)
ISRCTN no:	ISRCTN50098578
Design:	Multi-centre phase 2 randomised controlled trial
Overall aim:	To assess whether concurrent proton beam radiotherapy and chemotherapy significantly reduce the risk of grade 3 or above post-operative complications within 90 days of surgery, relative to concurrent photon beam radiotherapy (delivered as either intensity modulated radiotherapy (IMRT) or volumetric arc radiotherapy (VMAT)) and chemotherapy.
Primary endpoint:	Severe post-operative complications at 90 days post-surgery (grade 3 or higher by Clavien-Dindo criteria) and CTCAE v5.0 as included in the Esophageal Consensus.
Secondary endpoints:	• Evidence of Iso-Effectiveness, as measured by Pathologic Complete Response (pCR) rates and rate of clear margin resection (R0) • Disease-Free Survival • Overall Survival • Time from completion of neoadjuvant chemoradiotherapy to surgery • Number of patients who complete their radiotherapy regimen and reasons for non-completion. • Pre-surgery toxicity, and 30-day and 90-day post-operative mortality

	• Time from date of surgery to commencement of adjuvant systemic anticancer therapy (SACT) • Rate of completion of adjuvant systemic anticancer therapy (SACT) • Grade 4 Lymphopenia • Disease recurrence mapping for oligometastatic disease • Suitability to receive adjuvant systemic anticancer therapy (SACT) • Frequency of adverse events • Total toxicity burden (TTB) (calibrated to this study) 12 months from Chemoradiotherapy (CRT) • Quality of life (EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18) qualitative study of patient experience with proton beam therapy • Resource use and cost implications for health services, patients and their families, using the Participant Health Care Resource Use Questionnaire (modified Client Service Receipt Inventory (CSRI)), eCRFs including resource use information from interventions and other cancer therapies received by participants and electronic health records • Incremental cost-effectiveness analysis comparing costs and outcomes of Proton Beam Therapy vs photon-based radiotherapy, using EQ-5D-5L, eCRFs and resource use data
Exploratory Studies:	Translational analyses are planned (for patients with oesophageal adenocarcinoma [OAC] only) to identify whether response to Proton Beam Therapy-based CRT can be predicted from mRNA in pre-treatment formalin-fixed paraffin embedded (FFPE) biopsies. Whole blood for germline DNA will be collected after randomisation (before patients have started treatment) for future analysis. Cell free DNA (cfDNA) will also be collected post-study randomisation, and at up to 9 other time-points for future analysis. Patients with oesophageal squamous cell carcinoma (OSCC) will not be invited to participate in the exploratory research above. Additional translational analyses include an analysis of the acute impact of Proton Beam Therapy on

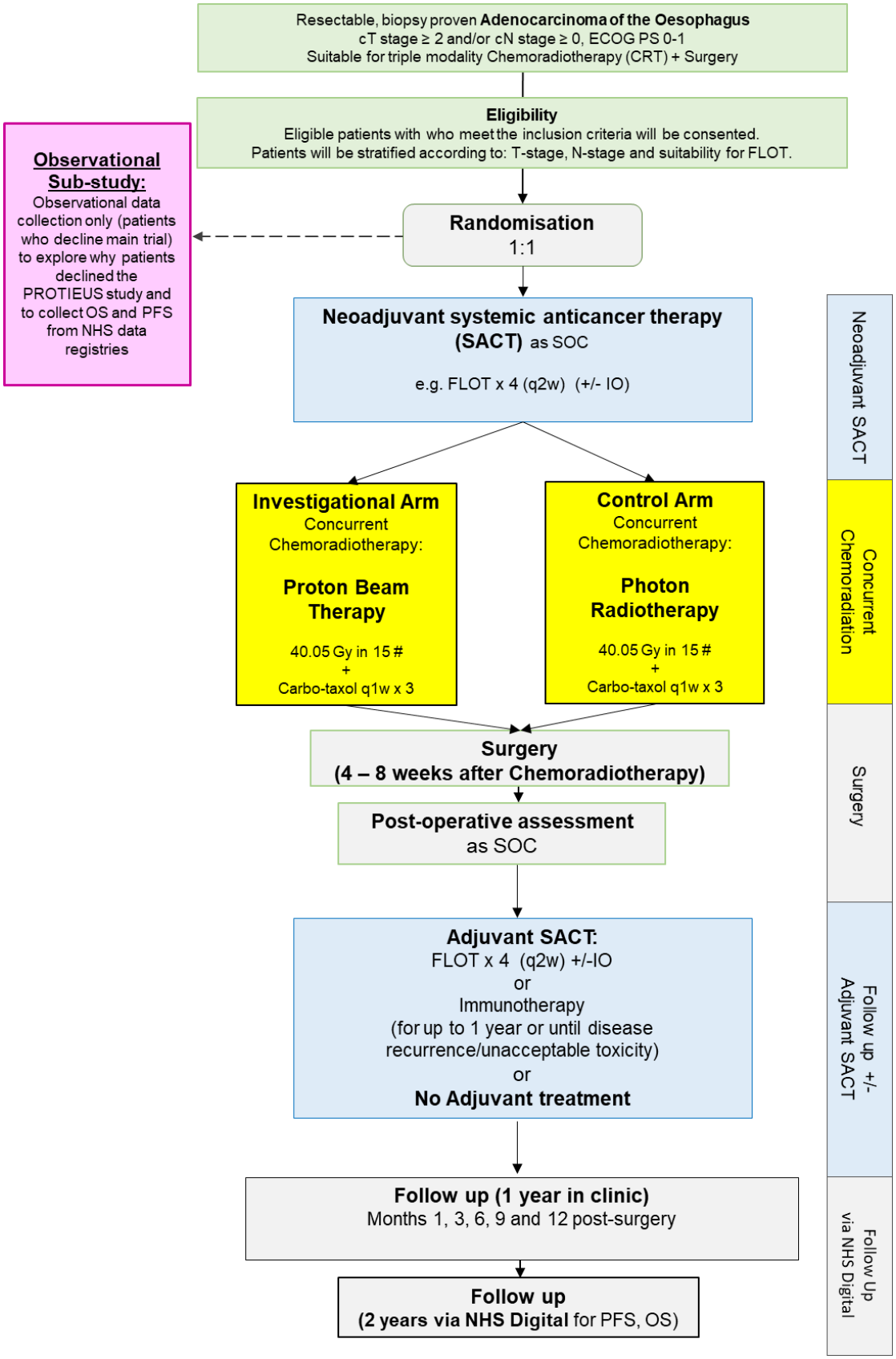
	cardiovascular structure and function using cardiovascular magnetic resonance (CMR) imaging and cardiopulmonary exercise testing prior to and following chemoradiotherapy.
Number of Sites:	10-15
Target accrual:	170 patients: • 130 oesophageal adenocarcinoma (OAC), • 40 oesophageal squamous cell carcinoma (OSCC)
Inclusion & exclusion criteria:	Main inclusion criteria: • Resectable, biopsy proven adenocarcinoma or squamous cell carcinoma of the oesophagus and the Gastroesophageal junction (GOJ) (max extension beyond GOJ of 3 cm) • cT stage ≥ 2 and/or cN stage ≥ 0-2 defined by AJCC 8th edition • ECOG performance status 0–1 • Adequate cardiovascular and respiratory function for surgery • Willing and able to receive treatment at a PBT centre if randomised to receive PBT treatment Main exclusion criteria • Metastatic or extensive nodal disease (N3) • Extension of tumour in to or involving cervical oesophagus or >3cm of stomach beyond the GOJ • Disease length (T+N) >14cm, for lower third tumours i.e. T and / or N extend below the diaphragm or T>10cm for middle third (thoracic tumours). *Please see full eligibility criteria in section 6.2.* • Previous treatment for oesophageal cancer • Unstable angina, uncontrolled hypertension, cardiac failure, arrhythmia or other clinically significant cardiac disease. • Medical comorbidity that would preclude surgery, chemotherapy, radiotherapy or immunotherapy • History of other malignancy likely to interfere with the protocol treatment or patients with active malignancy undergoing treatment

	A full list of inclusion and exclusion criteria can be found in section 6.2 (Patient Eligibility).
Treatment summary for Adenocarcinoma patients:	**<u>Adenocarcinoma patients</u>** in both arms will receive standard of care induction systemic anticancer therapy (SACT) as per local policy: e.g. 4 cycles FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel) +/- immunotherapy (IO) • Patients in the <u>interventional arm</u> will then receive concurrent proton based chemoradiotherapy comprising of three cycles of a weekly intravenous chemotherapy (e.g. carboplatin/paclitaxel), and 40.05Gy in 15 fractions Relative Biological Effectiveness (RBE) PBT. • Patients in the <u>control arm</u> will then receive concurrent photon-based chemoradiotherapy comprising of three cycles of a weekly intravenous chemotherapy (e.g. carboplatin/paclitaxel), and 40.05Gy in 15 fractions photon radiotherapy. Both arms will proceed to surgical resection. Following surgery, patients can receive SACT as per local policy, e.g.: • Up to 4 cycles of adjuvant FLOT chemotherapy And/or • Up to 1 year of adjuvant immunotherapy Or • No adjuvant treatment
Treatment summary for Squamous cell carcinoma patients:	**<u>Squamous cell carcinoma patients</u>** in both arms will receive standard of care induction systemic anticancer therapy (SACT) as per local policy: e.g. 2 cycles carboplatin and paclitaxel chemotherapy • Patients in the <u>interventional arm</u> will then receive concurrent proton based chemoradiotherapy comprising of 3 cycles of

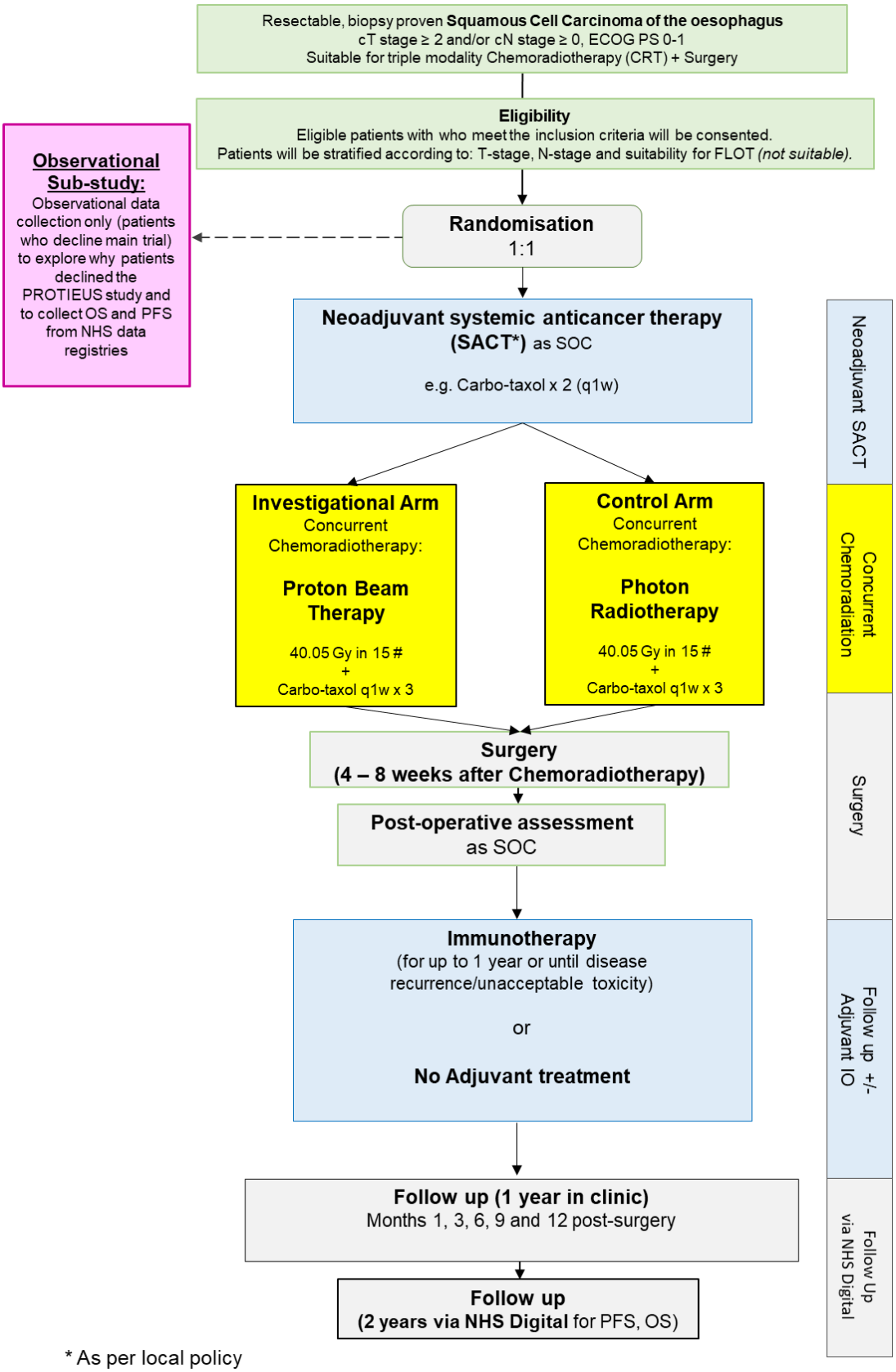
	a weekly intravenous chemotherapy (e.g. carboplatin/paclitaxel), and 40.05Gy in 15 fractions Relative Biological Effectiveness (RBE) PBT. • Patients in the control arm will then receive concurrent photon-based chemoradiotherapy comprising of 3 cycles of a weekly intravenous chemotherapy (e.g. carboplatin/paclitaxel), and 40.05Gy in 15 fractions photon radiotherapy. Both arms will proceed to surgical resection. Following surgery, patients can continue to receive SACT as per local policy: e.g.: • Up to 1 year of adjuvant immunotherapy Or • No adjuvant treatment
Duration of recruitment:	2.5 years
Duration of follow up:	Three years total: • 1 year at NHS Sites (during adjuvant IO if patients receive it) • 2 years via NHS Digital data registries
Definition of end of trial:	24 months after the last patients' follow-up
Observational Sub-Study:	Patients who do not consent to participate in the main trial will be invited to take part in the observational sub-study and be evaluated to understand patients' rationale for not pursuing a novel treatment option, and to assess whether this impacts patient outcomes. Approximately 65 patients will be registered to the observational sub-study. Survival data will be collected from NHS Digital for up to 3 years.

1.2 Trial Schema

1.2.1 Patients with adenocarcinoma:



1.2.2 Patients with squamous cell carcinoma:



* As per local policy

2 INTRODUCTION

2.1 Background

Oesophageal cancer [1] (OEC) comprising mainly oesophageal adenocarcinoma (OAC) and squamous cell carcinoma (OSCC) is one of the most lethal cancers with rising incidence and high mortality (1 in 18 cancer deaths). OEC ranked 7th in the incidence of cancer worldwide [2] in 2020 with 604,100 new cases, and 6th in mortality with 544,076 deaths attributed to OEC. Incidence rates of OAC are rising rapidly because of increased excess body weight and increasing gastroesophageal reflux disease. Although the optimal treatment strategy in OEC has been the subject of research for several decades (in which the United Kingdom (UK) leads across all disease stages: preoperative chemotherapy [3] and chemoradiation [4], definitive [5] and metastatic [6] settings), the “optimum strategy” has not yet been defined.

We are in an era in which combination therapies rather than surgery alone, are standard in the curative approach to patients presenting with locally advanced disease. A modern benchmark for 5-year survival approaches 50% [7], which is an approximate doubling over a 20-year time-period. This has been driven by the advent of preoperative concurrent neoadjuvant chemoradiotherapy (neoCRT) which has resulted in the median survival increasing from about 24 months to 49.5 months in the CROSS trial [8], and perioperative chemotherapy, which in the FLOT4 trial extended median survival to 50 months [9]. Multimodality treatment is necessary as 5-year overall survival (OS), for patients with locally advanced OC who undergo surgery alone, is low (range 23-33%) in contemporary studies [10, 11] with a significant risk of incomplete (R1) resection, local recurrence, and systemic dissemination. Radiation therapy is a critical component in the curative setting but incurs additional toxicity. Immunotherapy (IO) has further enhanced disease-free survival and is now standard of care after neoCRT and surgery in patients who do not achieve complete response

Based on that data, peri-operative standards of care in the UK for OAC have been: neoCRT with 41.4Gy/23 fractions – 45Gy/25 fractions radiotherapy (RT) concurrent with weekly paclitaxel and carboplatin, or pre-operative combination chemotherapy using a platinum-based regimen (FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel). In general, neoCRT is used in smaller tumours, or where the surgical margin is threatened and for patients unable to receive FLOT. Several randomised trials failed to identify the optimum strategy [12-14]. The largest, the Neo-AEGIS [15] (NCT01726452) trial – which compared ECX (epirubicin, cisplatin, capecitabine) or (2017 onwards) FLOT chemotherapy with CROSS chemoradiation (carboplatin/paclitaxel + radiotherapy 41.4Gy) reported similar survival between the two arms, noninferiority criteria were met with 3-year OS of 56% with CROSS and 57% with perioperative chemotherapy (hazard ratio [HR], 1.02; 95% CI, 0.74–1.42). Outcomes including rates of pathologic complete

response (pCR), resection clearance (R0), nodal downstaging and lesser haematological toxicity favoured CROSS [15].

Two major phase III trials have however altered the position of CRT vs FLOT in the peri-operative setting. Firstly, the Checkmate-577 study [16], which randomised SCC and OAC patients with incomplete pathological response following CRT then surgery to either: observation or 1 year of nivolumab. This showed a large disease free survival benefit (HR 0.69; 96.4% CI, 0.56 to 0.86; P<0.001), with similar benefit confirmed in the OAC subgroup (HR 0.75, 95%CI 0.59 – 0.96). The standard of care for patients receiving pre-operative CRT is therefore to receive a year of adjuvant nivolumab in the absence of pathological complete response.

More recently, abstract results of ESOPEC (NCT92509286) were announced at ASCO 2024 [17]. This study randomised resectable OAC patients (cT1 cNcM0 or cT2-4a cNany cM0) to either pre-operative CRT (without adjuvant nivolumab), or peri-operative FLOT. The results were strongly positive for the benefit of FLOT over CRT-alone, (Overall survival HR 0.70, 95% CI 0.53-0.92, p=0.012). Pathological complete response rates were higher with FLOT (19.3% vs 13.5%). Given Checkmate-577, 86.5% of CROSS patients would have been eligible for adjuvant nivolumab, making it uncertain if CROSS-IO is a worse option than FLOT alone (i.e. FLOT without the addition of IO).

Given the uncertainty in outcomes for this cohort of patients there is a justification and rationale to combine the known efficacious treatment options into a multimodal regimen. This would include a combination neoadjuvant phase of FLOT plus CRT; an area of significant research interest, currently being addressed by the ongoing randomised RACE trial (NCT04375605). However in the RACE trial, the post-operative treatment is 4 cycles of FLOT for all patients. Adjuvant chemotherapy is challenging, given only ~50% of patients completed adjuvant FLOT in the FLOT4-AIO, ESOPEC studies and FLOT + Durvalumab in the MATTERHORN trial compared to 86% who received at least 90% of the planned dose of adjuvant nivolumab. This is an area that may benefit from personalisation: those with pathological complete response could have adjuvant FLOT and IO, which is likely active for them given the pCR status. Those failing to achieve pCR could have adjuvant IO (squamous cell carcinoma) or FLOT-IO (adenocarcinoma): introducing a non-cytotoxic immunotherapy modality of treatment for those that have not responded fully to FLOT and CRT.

2.2 TOPGEAR and MATTERHORN

The TOPGEAR trial [18] was an international, phase 3 trial in which patients with resectable adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to receive preoperative chemoradiotherapy plus perioperative chemotherapy or perioperative chemotherapy alone (control). The GOJ cohort represented ~35% of the

cohort (574 recruited). No mention is made of a requirement on **total tumour length** (longitudinal extension) as an entry criteria and the preoperative chemoradiotherapy (CRT) **did not meaningfully increase treatment or surgical toxicity** compared with peri-operative chemotherapy alone. Whilst no higher rate of peri-treatment grade ≥3 toxicity or of major (grade ≥3) surgical complications in the CRT arm, a higher percentage of patients in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group had a pathological complete response (17% vs. 8%) and greater tumour downstaging after resection. At a median follow-up of 67 months, no significant between-group differences in overall survival or progression-free survival were noted. The median overall survival was 46 months with preoperative chemoradiotherapy and 49 months with perioperative chemotherapy (hazard ratio for death, 1.05; 95% confidence interval, 0.83 to 1.31), and the median progression-free survival was 31 months and 32 months, respectively. Treatment-related toxic effects were similar in the two groups. A trend toward poorer survival was noted among patients with tumours in the lower third of the stomach who had been assigned to preoperative chemoradiotherapy as compared with those who had upper-tract or gastroesophageal-junction tumours.

The MATTERHORN trial was a phase 3, double-blind, randomised trial [19], where participants with resectable gastric or gastroesophageal junction adenocarcinoma (the GOJ cohort was 25% of the 948 patients recruited, in a 1:1 ratio, to receive durvalumab at a dose of 1500 mg or placebo every 4 weeks plus FLOT for 4 cycles (2 cycles each of neoadjuvant and adjuvant therapy), followed by durvalumab or placebo every 4 weeks for 10 cycles. The primary endpoint was event free survival (EFS): the addition of durvalumab to FLOT demonstrated a statistically significant improvement in EFS compared to placebo plus FLOT. The hazard ratio (HR) for EFS was 0.71 (95% CI, 0.58–0.86; p<0.001), with median EFS not yet reached for the durvalumab group versus 32.82 months for the placebo group. At the time of analysis, median OS was also improved in the durvalumab group, although not statistically significant. The median OS was not reached for the durvalumab group, while the placebo + FLOT group had a median OS of 47.21 months (HR, 0.78; 95% CI, 0.62–0.97; p=0.025), suggesting that adding durvalumab may improve long-term survival, with further analysis needed at the final data cut-off. The safety profile of durvalumab + FLOT was tolerable, with no new safety signals identified and is another addition to the current standard of care.

2.3 Morbidity of triple modality approach

Oesophagectomy is a major treatment component in the curative management of OEC. It represents complex major surgery with significant risk of major morbidity, and a negative impact on Quality of Life (QoL). 90-day mortality and 90-day morbidity are established outcomes post-surgery across Europe [20, 21]. Reducing morbidity following neoCRT is a major research area because 65% of patients after oesophagectomy have grade 3+ complications by 90 days. The overall complications at 90 days are significantly higher when neoCRT is used [20] (65% vs 59%, P < 0.001). Pneumonia and leak from anastomosis are specific examples that occur more often compared to chemotherapy with respective, frequency of 21% vs 15%, P < 0.001 and 19% vs 11%, P <0.001.Postoperative pulmonary complications are the primary cause of postoperative

mortality, contributing to 45–55% of post-oesophagectomy deaths [22]. A prospective Danish [23] study showed that there is a high prevalence of cardiovascular disease in OEC and adverse cardiac events are frequent, occurring in ~25% of the patients within the 90-day follow-up period post treatment completion. Additionally, cardiac, and pulmonary toxicities are significant independent factors that influence both OS and disease-free survival (DFS) [24], and the ability to initiate timely adjuvant treatment.

2.4 Novel radiation technology: Proton Beam therapy

Conventional photon-based RT, which must enter and exit the body in order to reach the tumour, exposes normal tissues to significant doses of radiation, whereas Proton Beam Therapy (PBT) offers unique physical properties, characterised by the lack of an exit dose. This allows PBT to deliver a more conformal dose to the tumour and minimize the volume of normal tissue exposed to radiation. Initial studies have shown promising results with PBT for OEC, associated with reduced cardiac and lung toxicity [24] and reduced rates of grade 4 lymphopenia [25-27]. PBT is expected to have significant advantages for patients. There should be fewer postoperative complications and PBT could maintain normal immune function, both of which can improve overall survival. PBT may also improve survival due to non-cancer related mortality because mediastinal structures including the heart are spared.

2.5 Preclinical data/in silico modelling:

Despite heterogeneity between patients, the constant anatomical midline positions of oesophageal tumours relative to cardiopulmonary structures allows for meaningful/reliable dosimetry comparison between patients with tumours across published literature. *In silico* modelling of the potential benefit of PBT for oesophageal cancer in the last decade have demonstrated that a comparison of proton and photon-based plans for a given patient show substantial reduction in heart and lung doses with PBT, without compromising tumour coverage [28-31]. Our work [32] using planning CTs from patients treated in the UK completed SCOPE1 trial [5] revealed that the use of single-field optimisation spot scanning proton therapy was found to reduce the mean lung dose by 51.4% (range 35.1%–76.1%) and the mean heart dose by 40.9% (range 15.0%–57.4%), relative to photon-based volumetric modulated arc therapy. This implies that the potential benefits relating to normal toxicity reduction are likely to be clinically discernible. We have further shown that the toxicity reduction extends to bone marrow sparing [33] highlighting further potential benefits to the use of protons over photons that has recently been found to be an important factor in patient outcome. The dosimetric advantage associated with PBT may present an improved therapeutic ratio. PBT therapy may potentially provide an advantage to neoCRT + surgery when combined with IO in OEC. This is important because it remains unknown if the reduction in toxicity with proton neoCRT could facilitate timely delivery of adjuvant IO treatment and impact immune modulation due to reduced haematological system irradiation [26, 27].

Despite a large increase in the number of proton facilities worldwide in the last two decades (95 operational facilities), there are no reliable data from long-term randomised trials on survival, QoL, or functional capacity of patients who underwent PBT compared with any other treatment modality for any adult cancers. There are only 8 phase II & III randomised trials published [34], and the overall net health benefit of PBT versus its comparators cannot be fully assessed as studies have not consistently reported many outcomes of greatest interest [35]. PBT has been shown to be cost-effective for certain cancers including malignancies with poor prognosis such as locally advanced OC, in which tri-modality patients experience prolonged hospitalisations and there is an expected mortality rate from treatment induced toxicities. Baumann et al [36] has shown PBT was associated with a significantly lower relative risk of AEs within 90-days compared with CRT (grade 3+ relative risk 0.31, P= 0.002).

2.6 Clinical data

Our literature review [37] highlights a paucity of high-quality evidence supporting PBT use in OEC. Wide variation in intent and treatment protocols means that any role for PBT and a 'gold-standard' radiation protocol is yet to be defined. Current literature suggests significant benefit in terms of toxicity reduction, especially in the postoperative period, with comparable survival outcomes. One of the first series of 62 patients was reported by MD Anderson, with 76% of patients with adenocarcinoma, mostly located in the distal oesophagus/gastroesophageal junction (78%). All were treated with passive scattering (old technology) proton therapy and 2D Xray on treatment guidance to a median dose of 50.4 Gy /28 fractions [38]. Just under half (46.8%) of the patients were treated with preoperative chemoradiation, with 42% also receiving induction chemotherapy before chemoradiation. Grade 3 toxicities were <10%, with oesophagitis, nausea, and fatigue being the most common, and one grade 2 and one grade 3 pneumonitis. Another series using intensity modulated proton therapy delivered with pencil beam scanning (new technology) with a median dose of 50.4 Gy in 28 fractions concurrently with chemotherapy, reported acute grade 3 toxicity: oesophagitis and fatigue (16%). These examples are in stark contrast, despite the higher total dose delivered to any reported photon chemoradiation with or without surgery where reported grade ≥3 toxicity with photon chemoradiation is ≥50%. PBT in OEC holds significant promise for improving patient outcomes but requires robust systematic evaluation in prospective studies.

2.7 Current international proton trials

The PROTIEUS trial complements two important international trials (PROTECT and NRG GI006) that have recently started. However, this is the only study that uses a moderate hypofractionation, state of the art protons (pencil beam scanning and volumetric imaging during treatment) and includes IO as standard therapy post-surgery.

Comparison of the PROTIEUS study with two other PBT trials for OC

	UK (PROTIEUS)	EU (PROTECT)	USA (NRG GI006)
Status	Opened Q4 2024	EU2020 IMI2 Recruiting Q2 2022	NCI recruiting Q2 2019
Trial stage	Phase II	Phase III	Phase III
Adjuvant IO?	Yes (12 months)	No	No
Eligibility	OAC and OSCC Preoperative only	OAC and OSCC Preoperative (and definitive 10%)	OAC and OSCC Preoperative and definitive
Number	130 (OAC) 40 (OSCC)	397	300
IMRT arm (control)	40.05Gy 15F	41.4Gy 23F (60%) 50.4Gy 28F (40%)	50.4Gy 28F
Proton arm	40.05Gy 15F (RBE)	41.4GyE 23F(60%) 50.4GyE 28F (40%)	50.4GyE 28F
SACT	Carbo-taxol x 5 OR FLOT x 4 (neoadjuvant) +/- IO, carbo-taxol x 3, FLOT x 4 (adjuvant) +/- IO	Carbo-taxol x5 or (6 in 50.4 Gy arm)	Carbo-taxolx6 or FOLFOX
Centres	15 UK (2 proton centres new technology)	Proton centres (new and old technology) in 9 European countries	US proton centres (new and old technology)
Primary aim & endpoint for PBT	Improvement in 90-day grade 3-5 toxicity	Improvement in 90-day post-surgery or definitive CRT pulmonary complications	OS to be non-inferior (or superior) with less cardiopulmonary toxicity

2.8 Understanding the immune-biology in oesophageal carcinoma – an emerging role for RT

Immunotherapy has changed the treatment landscape in multiple cancers [39], but only a subset of patients show response to these treatments [40]. Thus, discovery of biomarkers determining who will benefit most is paramount. Most oesophageal cancer and gastro-oesophageal cancer immunotherapy trials have focussed on second- or third-line treatment of advanced/metastatic disease, and although encouraging, results have only shown modest survival increases compared with chemotherapy. Recently however, results from the CheckMate-577 trial, in which patients were treated with adjuvant Nivolumab following neoCRT and surgical resection, showed significantly increased disease-free survival compared to placebo [16]. Along with their direct cytotoxic effects, radiotherapy and chemotherapy can potentiate tumour immunogenicity [41]. The evidence, so far, indicates that some CRT regimens may induce immunogenic tumour cell death resulting in the release of tumour-antigens and pro-inflammatory mediators,

whose concerted action promotes the recruitment and activation of immune cells and enhances the activity of professional antigen presenting cells [42]. In post-neoadjuvant OEC patients, the number of CD8+ T-cells infiltrating the tumour has been shown to significantly increase after CRT, while only a small increase was observed after CT alone [43, 44].

Following neoadjuvant CRT, OAC surgical specimens have also been found to have dense IgG4+ plasma cell infiltration, with high numbers of IgG4+ plasma cells within CRT induced ulcers being associated with pathological response and improved survival [45]. IgG4+ plasma cells were present in CRT patients in significantly higher numbers than in those who went straight to surgery, a phenomenon potentially related to and dependent on the inflammatory response associated with CRT [45]. The immunomodulatory effects of CRT make their use in combination with immune checkpoint inhibitors of high therapeutic relevance. In OEC, PD-L1 positivity has been shown in 45% of tumours pre-neoadjuvant treatment, which increased to 77% post-CRT [43]. Furthermore, 50% of tumours changed status from PD-L1-negative to PD-L1-positive post-therapy [44]. In contrast, another study found no statistically significant difference between OEC PD-L1 expression and the administration of neoadjuvant therapy, however note, these patients received neoadjuvant chemotherapy only, which further supports a potential role for RT in potentiating tumour immunogenicity [46]. The immunomodulatory effects described may help explain the encouraging results of CheckMate-577 [16].

Further evidence of the additional benefit of IO comes from the MATTERHORN trial[19] where a benefit in EFS was achieved in the FLOT + durvalumab arm irrespective of the PDL1, Path CR or Nodal status.

A number of ongoing studies are evaluating immune checkpoint inhibitors therapy pre- and/or post-surgery either as monotherapy or concurrently with chemotherapy, chemoradiotherapy, and/or other immune checkpoint inhibitors. These include EA2174 (NCT03604991) and KEYNOTE-585 (NCT03221426),). These studies should be able to confirm observations of feasibility, safety, and efficacy of combinations. It is anticipated that biomarker analyses will provide further understanding on how to select biological characteristics in the population and thereby gain benefit from immune checkpoint inhibitors to optimise value and justify risks. Treatment individualisation and risk stratification biomarkers are urgently needed. Adenocarcinoma poses a particular challenge due to the high recurrence rate (52% within 1 year) resulting from seeding of undetected distant metastases at the time of diagnosis. Cancer-free (R0) resection margin, pCR) [47] and the absence of cancer involved lymph nodes [48] are all clinical factors associated with good survival of OEC.

In OEC biologically driven treatment personalisation may be possible in either the pre- and post-operative setting, based on selected radiological, molecular and pathological characteristics. The underlying biology is heterogeneous and whole-genome sequencing

studies have largely focussed on tissue samples taken at the time of surgery [47]. New methods, including the use of machine learning and artificial intelligence, are being applied to data sets to understand higher-order interactions between variables that better predict survival in OEC, but as yet, these are not ready for widespread application [49]. With advances in the sensitivity of ctDNA assays, metastatic subclones may be detectable in the blood, guiding indications for systemic therapy post-surgery [50], and helping to detect the heterogeneity of acquired resistance.

This evolution of practice in precision oncology for oesophageal cancer requires refinement to determine how we can further improve clinical outcomes further and faster. This includes improvements in both ensuring we maximise the utility of the known and new treatments in the current armoury, as well as optimising regimes to improve the therapeutic index, i.e., improving the outcomes, mitigating toxicity and limiting the treatment burden for patients.

This clinical trial aims to investigate if moderate hypofractionated chemo-proton beam therapy, integrated into the standard of care systemic anticancer chemotherapy (SACT) for locally advanced oesophageal adenocarcinoma and locally advanced oesophageal squamous cell carcinoma significantly reduces severe toxicity, including cardiopulmonary toxicity and permits timely initiation of adjuvant immunotherapy when compared with neoCRT delivered as part of triple modality therapy using intensity modulated radiotherapy, and whether this delivers value to the health care system and patients.

3 TRIAL DESIGN

This is a multi-centre, randomised controlled phase II trial of proton beam therapy (PBT) versus photon-based intensity modulated radiotherapy, delivered as either static fields (IMRT) or rotational fields (volumetric arc radiotherapy; VMAT). PBT will be delivered by either the Christie (Manchester) or the University College London Hospital (London) proton centres. Photon-based IMRT/VMAT will be delivered by the radiotherapy centre local to each patient. Similarly, surgery and follow-up will be conducted by local Sites. Following surgery, patients will be treated according to the local policy; for example, either adjuvant SACT (FLOT) with or without IO for up to 12 months, or just adjuvant IO for up to 12 months, or no adjuvant treatment. Patients will be followed up for 3 years. Follow-up for the last 2 years will be electronic data obtained from NHS Digital.

3.1 Trial Objectives

- To assess whether concurrent PBT and chemotherapy (carboplatin-paclitaxel) significantly reduces the risk of grade ≥3 post-operative complications within 90 days of surgery relative to concurrent photon RT and chemotherapy (carboplatin-paclitaxel).
- To obtain preliminary data on longer term efficacy outcomes following 1 year of adjuvant SACT for patients that do not achieve pathologic CR (PBT+ SACT vs photon RT+SACT), or adjuvant SACT for those that achieve pCR.

3.2 Trial Endpoints

3.2.1 Primary endpoint

- Severe post-operative complications at 90 days post-surgery (grade 3 or higher by Clavien-Dindo criteria [51, 52] & CTCAE v5.0 as included in the Esophageal Consensus [20]).

3.2.2 Secondary endpoints

- Evidence of iso-effectiveness as measured by Pathologic Complete Response (pCR) rates, and rate of clear margins resection (R0)
- Disease-free survival
- Overall survival
- Time from completion of neoadjuvant chemoradiotherapy to surgery
- Number of patients who complete their radiotherapy regimen and reasons for non-completion.
- Pre-surgery toxicity, and 30-day and 90-day post-operative mortality.
- Pre-surgery toxicity and radiotherapy completion rates measured from day 1 of neoadjuvant SACT

- Time from date of surgery to commencement of adjuvant SACT
- Rate of completion of adjuvant SACT
- Grade 4 Lymphopenia
- Disease recurrence mapping for oligometastatic disease
- Suitability to receive adjuvant SACT
- Frequency of adverse events
- Total Toxicity Burden (TTB) (calibrated to this study) 12 months from CRT
- QoL: EORTC QLQ-C30, QLQ-OES18, EQ-5D-5L, qualitative study of patient experience with proton beam therapy
- Resource use and costs for health system and patients and their families using the Participant Health Care Resource Use Questionnaire (modified Client Service Receipt Inventory (CSRI)), eCRFs including interventions and other cancer therapies and electronic health records
- Incremental cost-effectiveness analysis comparing costs and outcomes of PBT vs photon-based radiotherapy using EQ-5D-5L, eCRFs and resource use data

3.3 Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- ‘Adoption’ into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4 SELECTION OF SITES/SITE INVESTIGATORS

4.1 Site Selection

In this protocol trial 'site' refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol for the standard arm if not delivering proton therapy.
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority, and all amendments.
- Data collection requirements, including adherence to CRF submission timelines as per section 11.4 (Timelines for Data Entry).
- Biological sample collection requirements.
- Monitoring requirements, as outlined in protocol section 14 (Trial Monitoring and Oversight).
- Obtaining relevant licence(s) in relation to medical radiation exposure in the study, and renewing as necessary.

There will be two types of trial sites:

i) Local sites

These sites will undertake the following activities:

a. Assess eligibility, consent and enrol participants to the trial
b. Randomise participants
c. Perform standard of care chemotherapy, chemoradiation and immunotherapy treatment, surgery and follow up
d. Collect required clinical data and enter electronically onto OC database
e. Follow up participants for 1 year as per protocol
f. Collect biological samples and ship appropriately as per protocol/laboratory manual

ii) PBT treatment delivery centres (i.e. University College London Hospital (UCLH) and The Christie PBT centres).

These centres will undertake the following activities:

a. Plan and perform PBT for participants referred by the local sites
b. Provide standard of care chemotherapy treatment during the 3 weeks patients are treated with PBT
c. Collect required clinical data and enter electronically onto OC database
d. Collect biological samples and ship appropriately during PBT treatment as per protocol/laboratory manual

4.1.1 Selection of Principal Investigator and other investigators at sites

Each site must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of the site. Co-investigators must be trained and approved by the PI. All PIs and co-investigators must be medical doctors and have experience of treating oesophageal cancer. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI plans to take a leave of absence, UCL CTC **must be informed promptly.** For absences greater than three months, or where the PI is no longer able to perform their duties at the site, a new suitable replacement PI must be identified by the site and UCL CTC notified.

UCL CTC may terminate recruitment at a site where a suitable replacement PI has not been identified within three months.

4.1.2 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV for the PI must be forwarded to UCL CTC upon request.

4.2 Site Initiation and Activation

4.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by either an on-site visit or videoconference with site. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient.

4.2.2 Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- A signed and dated copy of the PI's current CV

In addition, the following agreement must be in place:

- A signed site agreement between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)

4.2.3 Site activation

Once the UCL CTC trial team has received all required documentation and the site has been initiated, notification of site activation will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol
- all relevant site staff are trained in the protocol requirements
- appropriate recruitment and medical care of patients in the trial
- timely completion of eCRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events
- that the site has facilities to provide **24 hour medical advice** for trial patients

5 INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheets, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent forms.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an independent interpreter/NHS approved translator would be required to ensure fully informed consent. If a patient requires an interpreter and none are available prior to consent, and for the duration of the potential participant's time on the trial, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheets for the trial should be discussed with the patient.

It is recommended a **minimum of twenty four (24) hours** is allowed for the patient to consider and discuss participation in the main trial. However, in order to prevent unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and implications. A member of the research team at the hospital must then phone the patient in the following days to confirm that they are still willing to participate in the trial.

Written informed consent on the current approved version of the consent form(s) for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient medical notes.

Patients that meet the eligibility criteria but decline to participate in the main trial should then be given the PIS and ICF for the observational sub-study.

Site staff are responsible for:

- checking that the current approved versions of the patient information sheets and consent forms are used
- giving the patient a copy of the patient information sheets (main study and observational sub-study)
- checking that information on the consent forms are complete and legible
- checking that the patient has completed all relevant sections and signed and dated the forms
- checking that an appropriate member of staff has countersigned and dated the consent forms to confirm that they provided information to the patient
- giving the patient a copy of their signed consent form
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)

- following randomisation, adding the patients' trial number to all copies of the consent forms, which should be filed in the patient's medical notes and investigator site file
- following randomisation, giving the patient a copy of the patient contact card

Sites may email/post the PIS to patients ahead of their appointment to allow for additional time to consider taking part in the trial. Further guidance on this will be provided at the Site Initiation Visit.

5.1 Remote consent

The option of **remote consent** will also be available to sites if it is not possible for consent to be taken in person. All steps performed need to be documented clearly and filed in patient notes accordingly. The delegated research team member from the trial site will approach the potential participant by telephone or by online teleconference (e.g. Zoom) to inform them of the trial and to discuss the trial. Patients will be provided with the main study participant information sheet (PIS) and the informed consent form (ICF) by email or post. If the potential participant wishes to take part, verbal consent can be obtained from them over the telephone/online teleconference by the delegated research team member, **in the presence of a witness**, at site without the need for the participant's signature, using the remote consent form. The delegated site staff taking consent will initial each clause as the patient agrees, and sign the consent form. The name of the witness will be documented on the remote consent form. The discussion and consent process must be documented in the participant's medical notes. Patients that consent remotely should email or post their completed remote consent form back to site, and then the investigator at site should sign and date the consent form and provide a copy to the patients and file a copy in their medical notes and in the ISF. This is in line with the HRA-MHRA joint statement on seeking consent by electronic methods, dated September 2018. A copy of the signed consent form will be posted to the participant by the study site.

Site staff are responsible for:

- Providing the current approved patient information sheet(s) and informed consent form(s) to the participant to review, via email or post.
- The PI or, where delegated by the PI, other appropriately trained site staff, must have a verbal conversation with the patient via a phone or video call (e.g. Zoom). The conversation must include a full explanation of the trial, all relevant treatment options and the current approved patient information sheet(s). The patient must have the opportunity to ask questions and the investigator must assess the patient's comprehension.
- Ensuring the patient has adequate time to consider the information. Therefore, the patient must have received the PIS(s) and ICF(s) before the phone or video call with the investigator. The patient should have the documents with them during the phone or video call.
- Guiding the patient through how to agree (or disagree if optional) to each item of the ICF(s). The investigator should guide the patient through which elements are mandatory for participation and which are optional.

- Documenting the entire consent process in the patient's medical notes, including:
    - Patient has confirmed verbally that they are happy to proceed to consent and that a discussion has been held
    - Version numbers of the PIS(s) and ICF(s) used
    - Date the PIS(s) and ICF(s) were emailed or posted to the participant
    - Date of the patient's signature: this is the date of consent.
- Explaining to the patient that they should initial, sign and date the ICF. They should email or post the completed ICF back to the investigator.
- Once received, the investigator should sign and date the ICF, and add the patient trial number to the ICF.
- The investigator should provide a fully completed copy of the ICF to the patient, file a copy in the patient's medical notes and file a copy in the ISF (with patient email if applicable).

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15 (Withdrawal of Patients).

6 SELECTION OF PATIENTS

6.1 Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record each patient screened for the trial/all patients identified with locally advanced oesophageal cancer considered for neoCRT followed by surgery and the reasons why they were not randomised in the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2 Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria must be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to randomising the patient. Confirmation of eligibility must be documented in the patients' medical notes and on the randomisation CRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1.1 (Pre-Randomisation Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1 Inclusion criteria

1. 16 years of age or older.
2. Histologically confirmed diagnosis of oesophageal adenocarcinoma (OAC) or oesophageal squamous cell carcinoma (OSCC).
3. Tumour of the thoracic oesophagus or gastroesophageal junction with distal maximum extension no more than 3 cm beyond the gastroesophageal junction.
4. cT stage ≥2 and/or cN stage 0-2 defined by AJCC 8th edition.
5. Tumour length based on position:
   a. Length of primary tumour ≤10cm in thorax, or
   b. ≤12cm in the gastroesophageal junction or lower third of the oesophagus, or
   c. Total length of disease (primary tumour and involved lymph nodes) length ≤14cm for lower third tumours.
6. ECOG performance status 0–1.
7. Suitable for and fit to receive curative neoadjuvant chemoradiotherapy followed by surgery by an Upper GI MDT.
8. Suitable for and fit to receive peri-operative immunotherapy according to local guidelines.
9. Adequate cardiovascular and respiratory function for surgery in the opinion of the surgical team within 4 weeks prior to randomisation.
10. Willing and able to give written informed consent and able to comply with treatment and follow up schedule.

11. Willing and able to undergo treatment at a PBT centre (i.e. UCLH or The Christie) if randomised to Proton Beam Radiotherapy (PBT) arm.

6.2.2 Exclusion criteria

1. Metastatic disease or extensive nodal disease (N3).
2. Patients who have had previous treatment for invasive oesophageal carcinoma or gastro-oesophageal junction carcinoma (including Photo Dynamic Therapy or laser therapy for high grade dysplasia/carcinoma in-situ).
3. Patients with >3cm mucosal extension of tumour into the stomach beyond the GOJ or where the superior extent is in the cervical oesophagus.
4. Tumour length based on position:
    a. Length of primary tumour >10cm in thorax, or
    b. >12cm in the gastroesophageal junction or lower third of the oesophagus, or
    c. Total length of disease (primary tumour and involved lymph nodes) length >14 cm for lower third tumours.
5. Patients with unstable angina, uncontrolled hypertension, cardiac failure or arrhythmia and other clinically significant cardiac disease.
6. Patients with an oesophageal stent (patients requiring a PEG/RIG/feeding jejunostomy for nutritional purposes ARE eligible).
7. No relevant co-morbidities, including Usual Interstitial Pneumonia (UIP) pulmonary fibrosis and connective tissue disorders.
8. History of other malignancy likely to interfere with the protocol treatment (e.g. patients with previously treated malignancy who have been disease-free for <1 year, or patients with active malignancy undergoing treatment).
    Exceptions:
    (a) Subjects who have been successfully treated and disease-free for >3 years,
    (b) a history of treated non-melanoma skin cancer,
    (c) successfully treated in situ carcinoma,
    (d) CLL in stable remission, or indolent prostate cancer requiring no or only anti-hormonal therapy.
9. Any other situation, which in the opinion of the local PI, makes the patient unsuitable for this trial.
10. Women who are pregnant or breastfeeding.
11. Patients unable to adhere to the contraception guidance in the protocol.

6.3 Pregnancy and birth control

6.3.1 Definitions

Definition of women of childbearing potential (WOCBP) and fertile men

A woman of childbearing potential (WOCBP) is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who:

- Has not undergone a hysterectomy or bilateral oophorectomy/salpingectomy

- Is not postmenopausal (a post-menopausal woman is a female who has not had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- Has not had premature ovarian failure confirmed by a specialist gynaecologist

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

6.3.2 Risk of exposure to trial treatment during pregnancy

The risk of exposure to trial treatment has been evaluated using the safety information available in individual SPCs for Carboplatin, Paclitaxel, Nivolumab and Durvalumab.

Overall, the trial treatment has been assessed as having a high risk of teratogenicity/fetotoxicity and genotoxicity.

6.3.3 Pregnancy testing

All female participants who are WOCBP must have a pregnancy test at screening and within 7 days of starting chemoradiotherapy treatment.

Additional pregnancy testing will be performed as per local policy and whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

6.3.4 Contraceptive advice

Requirements for female patients:
All female participants who are WOCBP must consent to use one of the following methods of highly effective contraception from randomisation until **6 months** after last dose of FLOT treatment or carboplatin/paclitaxel or nivolumab treatment (if received), or **3 months** after last dose of durvalumab, (if received), whichever is later. Methods with low user dependency are preferable, particularly where introduced as a result of participation in the trial.

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral (e.g. desogestrel)
  - injectable
  - implantable[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomised partner[1, 2]
- sexual abstinence[3]

1. Contraception methods that are considered to have low user dependency.

2. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

3. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Examples of effective (barrier) methods:

- Male condom
- Diaphragm
- Cervical Cap

For hormonal contraception methods that are not considered to have low user dependency, or may be susceptible to interaction with the trial treatments reducing the efficacy of the contraception method, a barrier method should be used in addition to the hormonal contraception, during the treatment period and for at least **6 months** after the last dose of trial treatment.

Requirements for male patients with female partners who are pregnant or WOCBP

Because of potential risk to the foetus when exposed seminal fluid:

Male patients (including male patients who have had vasectomies) must consent to use condoms with partners that are WOCBP or pregnant, during treatment and until **6 months** after last dose of FLOT treatment or carboplatin and paclitaxel treatment administration, whichever is later.

As nivolumab is not genotoxic and relevant systemic concentrations sufficient to produce a risk of foetal toxicity are not expected in WOCBP partners from exposure to male participant's seminal fluid, there is no requirement for male patients who have received nivolumab to use contraception beyond six months after their last dose of FLOT or carboplatin/paclitaxel treatment. There is no requirement for men to use contraception after durvalumab.

Male patients must also advise their partners that are WOCBP regarding contraceptive requirements as listed for female patients who are WOCBP.

For female and male patients:

The method(s) of contraception used must be stated in the patient medical notes. The medical notes of male participants should include a statement that the female partner has been informed about contraception advice.

6.3.5 Action to be taken in the event of a pregnancy

Female patients:

If a female patient becomes pregnant:

- **prior to initiating treatment:** the patient will not receive trial treatment and will be treated according to local policy

- **during treatment:** the patient will be withdrawn from further treatment and, if they consent to pregnancy monitoring, followed up until six weeks after the end of the pregnancy.
- **after the end of the treatment** but during the pregnancy at-risk period, the patient will be followed up until six weeks after the end of the pregnancy if they consent to pregnancy monitoring.

Male patients:

If a female partner of a male patient becomes pregnant, or a pregnant female partner is exposed to trial treatment between the patient's treatment start date and 6 months after the end of treatment, the male participant can continue with the study whilst their female partner will be followed up if they have given consent to pregnancy monitoring.

Notification to UCL CTC – refer to Pregnancy Report Processing (see Pharmacovigilance section 12.4).

6.3.6 Long term infertility

Radiotherapy is only limited to thoracic area and no long-term infertility is expected. Carboplatin may cause gonadal suppression resulting in amenorrhoea or azoospermia may occur in patients receiving antineoplastic therapy. The effects of leucovorin and paclitaxel on long term fertility are unknown, and the effect of nivolumab on male and female fertility is unknown. Fluorouracil, oxaliplatin and docetaxel my affect fertility in male patients, though the effect on female patients is unknown. Therefore, male and female patients should be offered advice on sperm or egg preservation, prior to initiation of the therapy, according to local policy.

7 RANDOMISATION & REGISTRATION PROCEDURES

7.1 Randomisation to the Main Study

Patient randomisation will be undertaken by Sites via a remote data capture system hosted by UCL CTC (OC), and this must be performed prior to commencement of any trial treatment. Please refer to the randomisation procedure document in the ISF for full guidance on patient randomisation.

Site staff responsible for patient randomisation must request access to the OC database from the UCL CTC, and being assigned this responsibility on the site staff delegation log by the PI. Access to the OC database will be provided by UCL CTC.

Patients will be randomised to the main study using a 1:1 allocation ratio. Patients will be stratified according to the following information using minimisation:

- T-stage and
- N-stage and
- FLOT suitability

Following consent to the main study, pre-randomisation evaluations (as detailed in section 9.1.1 [Pre-Randomisation Assessments]) and confirmation of eligibility of a patient at a site, the randomisation form must be fully completed on the OC database. This will be used by UCL CTC to confirm patient eligibility. If further information is required UCL CTC will contact the person requesting randomisation to discuss the patient and request forms to be updated on the system.

Patients' name, date of birth, NHS number, postcode, gender, ethnicity and telephone number/email are required to randomise a patient. Once eligibility has been confirmed a trial number and treatment allocation will be assigned for the patient.
UCL CTC will email confirmation of the patient's inclusion in the trial, their trial number and treatment allocation to the PI, lead contact at the radiotherapy and surgical Site, and the Proton Beam Centre contact and PI if allocated the PBT arm. The trial number must be recorded in the patients notes.

Sites should contact UCL CTC if there are any difficulties in accessing the randomisation database.

UCL CTC Telephone number for queries relating to Randomisation:	**0207 679 9608**
PROTIEUS email address:	**ctc.protieus@ucl.ac.uk**
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Once a patient has been randomised onto the main trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient contact card. Site contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial.

After randomisation into the main trial, the patient's general practitioner (GP) should be informed of the patient's involvement in the trial by the site completing and sending the completed GP letter.

For patients randomised to the PBT arm of the trial, sites must refer the patient to a PBT centre via the portal, on the day of randomisation (refer to randomisation procedure document).

7.2 Registration to the Observational Sub-Study

Patients that meet the eligibility but decline to participate in the main study should be provided with a PIS and ICF for the observational sub-study to help explore the reasons patients decline the trial and to enable us to follow-up the patients and collect survival data via data registries (NHS Digital).

Patient registration to the observational sub-study will be undertaken by Sites via a remote data capture system hosted by UCL CTC (OC). Please refer to the registration procedure document in the ISF for full guidance on patient registration for the observational sub-study. Approximately 65 patients will be registered to the observational sub-study.

Site staff responsible for patient registration must request access to the OC database from the UCL CTC and being assigned this responsibility on the site staff delegation log by the PI. Access to the OC database will be provided by UCL CTC.

Following consent to the observational sub-study, no assessments are required, and the consent form eCRF can be fully completed on the OC database. This will be used by UCL CTC to confirm patient eligibility. If further information is required UCL CTC will contact the person requesting registration to discuss the patient and request forms to be updated on the system.

Patients' initials, date of birth, NHS number, postcode, gender and ethnicity are required to register a patient on the observational sub-study. Once eligibility has been confirmed, UCL CTC will email confirmation of the patient's inclusion in the trial and their trial number to the PI and lead contact at Site***.*** The trial number must be recorded in the patients notes.

Sites should contact UCL CTC if there are any difficulties in accessing the registration database.

UCL CTC Telephone number for queries relating to Registration:	**0207 679 9608**
PROTIEUS trial email:	**ctc.PROTIEUS@ucl.ac.uk**
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Once a patient has been registered onto the observational sub-study they must be provided with the following:

- A copy of their signed consent form and patient information sheet

8 TRIAL TREATMENT

8.1 Treatment Summary

All patients will be randomised to either proton or photon radiotherapy with neoadjuvant and concurrent systemic anticancer therapy (SACT). All patients should start their first cycle of chemotherapy within 3 weeks (21 days) following randomisation. Patients who have been declared suitable for FLOT by an oncologist before randomisation will receive up to 4 cycles of neoadjuvant SACT: FLOT (Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel) chemotherapy, with/without neoadjuvant immunotherapy as per local guidelines. Patients who are not suitable for FLOT will receive two weekly cycles of neoadjuvant chemotherapy (i.e. carboplatin and paclitaxel, given weekly) given as per local guidelines.

Patients in the ***interventional arm*** will then receive concurrent proton based chemoradiotherapy and patients in the ***control arm*** will then receive concurrent photon-based chemoradiotherapy. Radiotherapy (proton or photon) will be given at a dose of 40.05Gy in 15 fractions over 3 weeks, 5 fractions per week. Concurrent weekly IV chemotherapy (e.g. carboplatin and paclitaxel) will be given for 3 cycles during radiotherapy.

After chemoradiotherapy, patients in both arms will proceed to surgical resection. Four to twelve weeks after surgery, patients can receive standard treatment as per local policy: for example, up to 4 cycles of adjuvant FLOT chemotherapy and/or adjuvant immunotherapy, or no adjuvant treatment. Immunotherapy will be given as per local policy until patients have disease recurrence, unacceptable toxicity or have received a year of immunotherapy treatment, whichever happens first.

Patients may receive standard treatment as per local guidelines peri-operatively, e.g. the following treatments in this trial are standard of care for the treatment of oesophageal cancer and are not considered Investigational Medicinal Products. They will be given according to local policy and supplied from hospital commercial stock, prepared and administered according to local guidelines. Sites should use the current summary of product characteristics (SPC) for clinical management information including information on toxicities, stability and administration. No chemotherapy/immunotherapy drug accountability is required:

- Carboplatin
- Paclitaxel
- Immunotherapy (e.g. Nivolumab or Durvalumab)
- FLOT (Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel)

Photon radiotherapy (RT) is considered standard of care in this trial and will be given according to the PROTIEUS Radiotherapy and QA Guidance document and administered according to local guidelines:

- Photon Radiotherapy (RT)

The investigational treatment is:

- Proton Beam Radiotherapy (PBT)

The PROTIEUS Radiotherapy and QA Guidance document must be used in conjunction with the PROTIEUS protocol.

Surgery is standard of care for this trial (see section 8.2.3).

8.1.1 PBT Arm

Patients randomised to the PBT arm will be given an outpatient assessment and planning CT visit in either The Christie or UCLH NHS PBT centres as soon as possible following randomisation and within 4 weeks of the expected start date of chemoRT.

PBT will be given at a dose of 40.05Gy in 15 fractions (relative biological effectiveness [RBE]) over 3 weeks.

Patients will receive their neoadjuvant chemotherapy +/- IO at their local centre, except for the 3 weeks of chemotherapy that is given concurrently with radiotherapy, which will be given at the allocated PBT centre.

Adjuvant SACT (immunotherapy and/or chemotherapy) will be delivered at local centres.

8.1.2 Photon Arm

Patients randomised to the photon arm will receive their radiotherapy and chemotherapy +/- IO treatments at their local centre. A planning CT visit should be performed as soon as possible following randomisation and within 4 weeks of the expected start date of chemoRT.

Photon radiotherapy (IMRT/VMAT) will be given at a dose of 40.05Gy in 15 fractions over 3 weeks.

Adjuvant SACT (immunotherapy and/or chemotherapy) will be delivered at local centres.

8.2 Treatment Scheduling

8.2.1 Neoadjuvant Systemic Anticancer Cancer Therapy (SACT)

For patients with adenocarcinoma, induction SACT e.g. FLOT should be given as 2-weekly cycles (i.e. every 2 weeks) as per the local policy, for up to 4 cycles. Dose reductions or adjustments made to the FLOT regimen to improve patient tolerability according to local policy are permitted. Immunotherapy, if administered (e.g. Durvalumab), is recommended to be given 4-weekly, starting on day one of FLOT (2 cycles of Durvalumab to be given pre-surgery) as per the local policy.

For patients with squamous cell carcinoma, induction SACT should be given as 2 cycles of weekly IV chemotherapy, according to sites' local policy (e.g. weekly IV carboplatin and paclitaxel).

8.2.2 Chemoradiation

Neoadjuvant chemotherapy should be followed by concurrent weekly chemotherapy infusions, (e.g. carboplatin and paclitaxel given intravenously) on Day 1, 8 and 15 of radiotherapy.

For adenocarcinoma patients suitable for FLOT, concurrent chemoradiotherapy should aim to start 2-4 weeks after the start of the final cycle of FLOT.

For squamous cell carcinoma patients and adenocarcinoma patients unsuitable for FLOT, concurrent chemoradiotherapy should aim to start 1 week after the 2 cycles of neoadjuvant weekly chemotherapy, i.e. 5 consecutive weeks of chemotherapy (e.g. carboplatin and paclitaxel). They will be given weekly chemotherapy infusions according to sites' local policy, (e.g. carboplatin and paclitaxel given intravenously) on day 1, 8, 15, 22 and 29 (+/-1day acceptable to account for bank holidays or other unpredicted situations).

Radiotherapy must be given on continuous weeks once it starts.

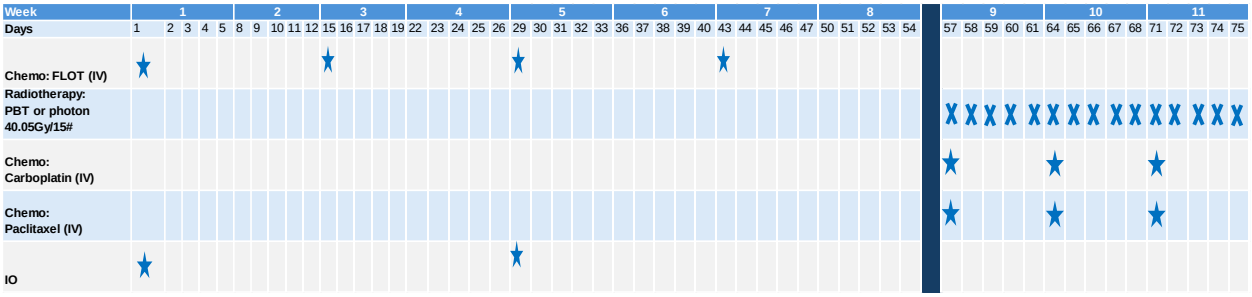
Example Schedules:

For squamous cell carcinoma patients and adenocarcinoma patients not suitable for FLOT chemotherapy an example of accepted scheduling is outlined below:
Carboplatin and paclitaxel (given intravenously) on day 1 and 8 and then concurrently with radiotherapy on day 15, 22 and 29.

Week	1					2					3					4					5				
Days	1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	23	24	25	26	29	30	31	32	33
Radiotherapy: PBT or photon 40.05Gy/15#											X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemo: Carboplatin (IV)	★					★					★					★					★				
Chemo: Paclitaxel (IV)	★					★					★					★					★				

An example of accepted scheduling is outlined below for patients with adenocarcinoma suitable for FLOT chemotherapy:
FLOT chemotherapy (given intravenously) every 2 weeks: on days 1-2, 15-16, 29-30 and 43-44. If administered, IO e.g. Durvalumab, will be given on day 1 and day 29.
Then a 2-week gap (although up to a 4-week gap is acceptable).

Carboplatin and paclitaxel (given intravenously) weekly on days 57, 64 and 71.



8.2.3 Surgery

Patients will proceed to surgical resection ideally within 4-8 weeks of completing CRT.

The following surgical approaches (either minimally invasive or open) will be permitted: 2-phase (right thoracotomy, laparotomy), 3-phase (right thoracotomy, laparotomy, cervical incision), and thoracoabdominal. Use of a transhiatal approach is prohibited. Lymphadenectomies along the common hepatic artery, left gastric and splenic artery (either *en bloc* or separately) will be performed, and the pericardial fat pad and strips of pleura will be removed. Crural fibres and a cuff of diaphragm will be removed if required for tumour clearance. The para-oesophageal and diaphragmatic nodes will be removed in continuity with the oesophagus. The lymph nodes at the tracheal bifurcation and along the right and left main bronchi to the pulmonary hilus will be removed (*en bloc* or separately).

8.2.4 Adjuvant SACT

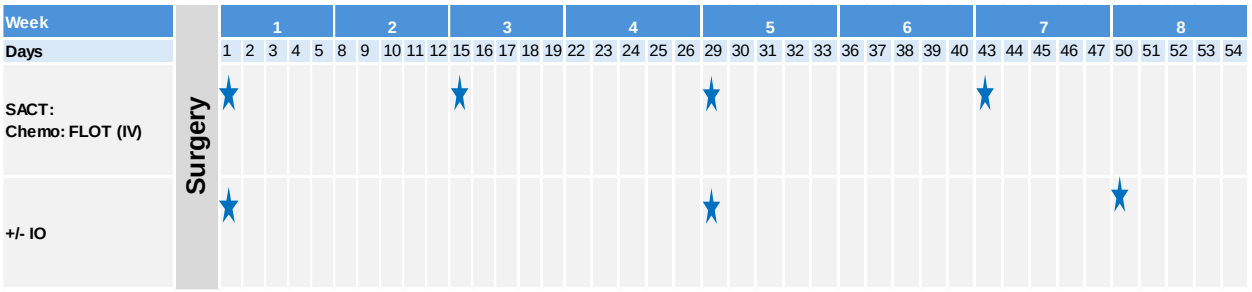
Following surgery, patients can receive adjuvant SACT as per local policy. Adjuvant treatment may begin 4 to 12 weeks post-surgery. Patients must have sufficiently recovered from surgery before starting adjuvant SACT.

8.2.4.1 Adjuvant Immunotherapy

Adjuvant immunotherapy should be delivered according to sites' local policy, (e.g. Nivolumab or Durvalumab) until disease recurrence, unacceptable toxicity or until a year of treatment has been administered.

8.2.4.2 Adjuvant Chemotherapy

For patients that have received FLOT (+/-) IO prior to surgery, investigators may offer patients up to 4 cycles of adjuvant chemotherapy, as per local policy. If given, IO (Durvalumab) will be given 4-weekly initially, with FLOT then continued up to a total of 10 cycles (12 cycles in total with the 2 doses given preoperatively).
Adjustments to the standard of care FLOT regimen as per local policy to improve tolerability are permitted.



8.2 General Principles Relating to Radiotherapy

Patients should ideally start radiotherapy on a Monday or Tuesday. Local centres may choose to give chemotherapy treatment starting on day 1 or 2 of radiotherapy e.g. to avoid Bank Holidays (for example if radiotherapy starts on a Tuesday, then chemotherapy may be given on a Tuesday (day 1 of radiotherapy) or Wednesday (Day 2 of radiotherapy). Weekly (carboplatin and paclitaxel) chemotherapy should be given on the same day each week (+/- 1 day). In exceptional circumstances (e.g. machine break down/machine service/bank holidays) follow local hospital policy.

When an interruption to radiotherapy treatment occurs for any reason (e.g. due to AEs or bank holidays) the radiotherapy prescription remains unchanged (i.e. the dose prescribed remains as planned with the same number of fractions even if this is delivered over a longer treatment time). Additional fractions should NOT be given on the same day.

8.2.4 Radiotherapy Delivery

The key elements of the radiotherapy protocol are outlined below, and full radiotherapy guidelines are provided in the PROTIEUS Radiotherapy Planning Guidance Document. **The PROTIEUS Radiotherapy and QA Guidance document must be used in conjunction with the PROTIEUS protocol.**

8.2.5 Dose prescription

Patients will be randomised to either proton or photon chemoradiotherapy. Both treatment arms will have the same dose fractionation (40.05Gy/15#) over 3 weeks.

8.2.6 Target Volume and OAR delineation

Target volume delineation (GTV and CTV) and OAR delineation will be identical for both radiotherapy arms. Diagnostic information should be taken from the diagnostic CT scan, PET-CT and EUS (if available). Auto-segmentation techniques should not be used for target volume delineation. In certain situations, particularly around GOJ, the EUS length may not accurately match up with the CT slices, as the tumour inclines forward (so if one is counting down CT slices, this will be 'shorter' than the actual EUS length). CTVA and CTVB will be generated according to PROTIEUS Radiotherapy Planning Guidance Document.
For protons plans, no PTV will be generated. Instead, PBT treatment plans will optimised and evaluated in against pre-defined uncertainty scenarios which will account for

expected setup and range uncertainties. Photon plans will have PTVs generated. Treatment plans will be optimised to PTV.

The organs at risk (OARs) that must be contoured for PROTIEUS and the naming convention used in naming these structures are detailed in the Radiotherapy Planning Guidance Document.

The spinal cord should be outlined on slices which include, or are within, 20mm of the PTV in the superior and inferior directions and a Planning Risk Volume (PRV) for the cord is created to account for positioning error.

The lungs, heart (excluding major vessels), liver, stomach and both kidneys (if either are coincident with the PTV), spleen must also be outlined.

Example of heart and stomach outlining are also provided in the Radiotherapy Planning Guidance Document.

8.2.7 CT Simulation and immobilisation

A contrast enhanced CT (CECT) in treatment position will be acquired for RT planning. A 4DCT is mandated for all cases. Please refer to Radiotherapy QA Guidance document for more details.

CT slice thickness should be no greater than 3mm. Intravenous contrast should be used (providing adequate renal function), but oral contrast should not be used. Patients should be adequately immobilised for CT simulation scan and treatment as per departmental protocol. Additional immobilisation to minimise breathing motion is recommended, e.g. abdominal compression belts. Treatment in breath-hold is not recommended.

8.2.8 Treatment Plan Optimisation

A single phase inverse-planned IMRT or VMAT treatment plan should be produced for all patients randomised to the photon arm. Type B algorithms (e.g. collapsed cone, AAA) must be used for dose calculation. Proton planning will be carried out by physicists in PBT centres with experience in proton planning.

Full details of dose objectives, optimisation strategy and standardised nomenclature is provided with the Radiotherapy Guidance Document.

8.3 Radiotherapy Trials Quality Assurance (RTQA)

RTQA guidance for PROTIEUS has been developed in conjunction with the National RTTQA Group and is included in the PROTIEUS Radiotherapy and QA Guidance Document. There will be RTQA for both photon and proton arms.

8.3.4 Pre-accrual Quality Assurance

There is a full programme of pre-accrual quality assurance including the completion of an outlining exercise and planning exercise. Pre-accrual RTQA will be streamlined for clinicians and centres who have previously completed RTQA exercises for the SCOPE2 and NeoSCOPE trials. All pre-accrual QA is completed prior to centre activation for the PROTIEUS trial.

8.3.5 On Trial Quality Assurance

There will be prospective individual case review of outlines for:

- at least the first 3 patients in the photon arm recruited at each centre
- at least the first 3 patients in the proton arm recruited at each PBT centre
- further cases at the discretion of the RT QA team

There will be prospective individual case review of the plans for:

- at least the first patient in the photon arm recruited at each centre
- at least the first 3 patients in the proton arm treated at each PBT centre with UK peer review.
- further cases at the discretion of the RT QA team

8.4 Clinical Management after Treatment Discontinuation

If a patient discontinues trial treatment early, they will remain on trial for follow up purposes unless they explicitly withdraw consent. Also refer section 9 [Assessments] and section 15 [Withdrawal of Patients] for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

8.5 Management of Overdoses, Research Procedure Error, or Occupational Exposure

Overdose

Overdose is administration of a quantity of a research procedure, either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as overdose by the trial team at site or by the Sponsor upon review.

Overdoses should be reported on an incident report (see section 13.1). Any adverse events resulting from an overdose should be reported as an SAE (see section 12.2.3 for reporting procedures).

Research Procedure error

A research procedure error is any unintentional error in prescribing, dispensing, or administration of research procedure while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by the Sponsor upon review.

If the research procedure error is an overdose, refer to the section above. Otherwise research procedure errors should be reported on an incident report (see section 13.1). Any adverse events resulting from a research procedure error should be reported as an SAE (see section 12.2.3 for reporting procedures).

Occupational exposure

Exposure to radiation as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 13.1).

9 ASSESSMENTS

9.1 Main Study:

Please also refer to Quick Reference Guide to Patient Visits table in Appendix 1.

9.1.1 Pre-Randomisation Assessments

Patients must give written informed consent **before** any trial specific screening investigations may be carried out.

The following assessments or procedures are required to evaluate the suitability of patients for the trial:

- Histological confirmation of adenocarcinoma or squamous cell carcinoma of the oesophagus or GOJ.
- Documented Upper GI MDT discussion confirming eligibility as per the above inclusion/exclusion criteria
- Dihydropyrimidine dehydrogenase (DPYD) testing for patients with adenocarcinoma (test must be performed prior to randomisation as per local policy, and results must be known before treatment starts).
    - Patients with adenocarcinoma showing no detected DPYD deficiency will be treated with FLOT chemotherapy as per local policy.
    - Patients with adenocarcinoma with heterozygous DPYD deficiency can be treated with a reduced dose of FLOT chemotherapy as per local policy.

Strongly recommended within 6 weeks prior to randomisation:

- Endoscopic ultrasound (strongly recommended, but not mandatory) and laparoscopy (as per institutional standard of care for GOJ tumours)

Within 4-6 weeks prior to randomisation (at least 1 of the below scans must be within 6 weeks prior to randomisation):

- Whole body PET-CT

  and
- CT (Thorax, Abdomen and Pelvis), (contrast enhanced, neck optional)

Within 12 weeks prior to randomisation:

- Pulmonary function test (e.g. cardiopulmonary exercise testing such as CPEX/CPET or lung function tests).
- Cardiac function testing (e.g. ECG and ECHO or MUGA) according to local policy
    - *If it is not possible to perform cardiopulmonary function tests before randomisation, tests must be performed before treatment starts.*

Within 7 days prior to randomisation:

- Relevant medical history, assessment and documentation of baseline AEs (according to CTCAE v5)
- Full physical examination (to include height and weight)
- Vital signs (BP, heart rate, temperature)
- Mellow dysphagia swallowing score (refer to Appendix 5)
- ECOG performance status (refer to Appendix 3)
- Full Blood Count and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)
- Serum biochemistry, renal and liver function (albumin, lactate dehydrogenase (LDH), urea, creatinine, sodium, potassium, bilirubin, aspartate transaminase (AST) and/or alanine transaminase (ALT))
- Pregnancy test for WOCBP

9.1.2 Pre-Neoadjuvant SACT Assessments

Patients should start neoadjuvant SACT within 21 days of randomisation. Patients should not start treatment unless all eligibility criteria remain fulfilled.
Patients randomised to the interventional (PBT) arm will attend a planning visit at the allocated PBT centre (i.e. UCLH or The Christie), and patients randomised to the control (Photon radiotherapy) arm will attend a planning visit at their local centre.

Within 7 days prior to starting neoadjuvant SACT:

- Pregnancy test for WOCBP as per standard of care prior to starting treatment. (If a pregnancy test was performed pre-randomisation and is within 7 days prior to start of treatment this test does not need to be repeated).
- Participant Health Care Resource Use Questionnaire (Modified Client Service Receipt Inventory (CSRI))
- QoL questionnaires (EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18)

Research Samples (Adenocarcinoma patients only):

- CfDNA and germline DNA blood samples for exploratory research [refer to section 10 Exploratory Translational Studies]. <u>These blood samples must NOT be taken before patients have been randomised.</u>

9.1.3 Assessments during Neoadjuvant SACT

During neoadjuvant SACT, clinical assessment should be performed:

- Every 2 weeks for patients receiving FLOT+/-IO
- Every 1 week for patients receiving weekly carboplatin-paclitaxel chemotherapy

Blood tests should be performed within three days of each chemotherapy cycle.

Neoadjuvant SACT assessments should include:

- Review of AEs (according to CTCAE v5)
- Weight
- Full physical examination (cycle 1)

- Mellow dysphagia swallowing score (refer to Appendix 5)
- ECOG performance status (refer to Appendix 3)
- Full Blood Count and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)

9.1.4 Pre-Chemoradiation Assessment

Clinical assessment should be performed within 7 days prior to commencing CRT.

- For patients not suitable for FLOT this will be during week 2 of neoadjuvant carboplatin-paclitaxel.
- For patients suitable for FLOT it will be during the gap between the final cycle of FLOT and commencement of chemoradiation.

- Review of AEs (according to CTCAE v5)
- Weight
- Targeted physical examination
- Mellow dysphagia swallowing score (refer to Appendix 5)
- ECOG performance status (refer to Appendix 3)
- Full Blood Count and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)
- EQ-5D-5L QoL questionnaire

Research Samples (Adenocarcinoma patients only):

- CfDNA blood sample for exploratory research

9.1.5 Assessments during concurrent Chemoradiation Treatment

Clinical assessments should be performed weekly during the 3 weeks of concurrent CRT treatment. Blood tests should be performed within three days of each chemotherapy cycle.

Patients randomised to the interventional (PBT) arm will receive 3 of the 5 weeks of chemotherapy that is concurrent with PBT and also have the assessments below at the allocated PBT centre (i.e. UCLH or The Christie).

Weekly assessments during concurrent CRT should include:

- Review of AEs (according to CTCAE v5)
- Weight
- Targeted physical examination
- Mellow dysphagia swallowing score (refer to Appendix 5)
- ECOG performance status (refer to Appendix 3)
- Full Blood Count and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)
- Serum biochemistry, renal and liver function (albumin, lactate dehydrogenase (LDH), urea, creatinine, sodium, potassium, bilirubin, aspartate transaminase (AST) and/or alanine transaminase (ALT))

9.1.6 Completion of Chemoradiation Treatment

The following should be carried out between 4-6 weeks after the last fraction of radiotherapy:

- PET-CT (only if clinically indicated)
- CT (Thorax, Abdomen and Pelvis), (contrast enhanced, neck optional)
- Review of AEs (according to CTCAE v5)
- Targeted physical examination
- Mellow dysphagia swallowing score (refer to Appendix 5)
- ECOG performance status (see Appendix 3)
- Cardiac function testing e.g. ECG
- Pulmonary function test (not mandatory but strongly recommended) (e.g. CPEX/CPET or lung function tests
- Full Blood Count and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)
- Participant Health Care Resource Use Questionnaire
- EQ-5D-5L QoL questionnaire

Research Samples (Adenocarcinoma patients only):

- CfDNA blood sample for exploratory research

9.1.7 Assessments at surgery:

Surgery is performed as standard of care for the PROTIEUS trial, (refer to section 8.2.3 for details), and data from surgery will be reported on the eCRFs.

Surgical photographs will be collected as part of the Surgical QA of the trial; please refer to section 17 and the Surgical QA Guidance Document in the ISF for full details.

9.1.8 Assessments for patients who do not have surgery:

Patients that do not have surgery should come off trial and followed-up according to sites' local policy.

The following events should be reported:

- Disease recurrence
- Death

Patients that do not have surgery should complete an EQ-5D-5L before coming off trial.

9.1.9 Assessments during Adjuvant SACT

Within 4-12 weeks after surgery, patients may commence adjuvant SACT: up to 4 cycles of adjuvant FLOT chemotherapy and/or immunotherapy treatment (within 4-12 weeks after surgery) for up to 1 year (see section 8.2.4), or no adjuvant therapy, as per local policy. Assessments will be performed fortnightly during adjuvant chemotherapy. Assessments during adjuvant immunotherapy will be according to section 9.1.10 below.

Blood tests should be performed within three days of each adjuvant chemotherapy cycle.

Adjuvant SACT assessments should include:

- Review of AEs (according to CTCAE v5)
- Weight
- Targeted physical examination
- ECOG performance status (refer to Appendix 3)
- Full Blood Count and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)

9.1.10 Assessments During Follow Up

Follow-up assessments will be at 1, 3, 6, 9 and 12 months (from the date of surgery) at NHS sites. Follow-up data will also be collected for a further 2 years via NHS Digital data registries.

Patients that do not receive adjuvant SACT (IO/chemotherapy) treatment should also be followed-up after surgery.

All efforts should be made by the Site to contact the patient's GP to assess their condition if a patient fails to attend a clinic or cannot be followed up at site.

9.1.10.1 Follow-up Month 1

The following should be carried out 4 weeks (+/- 14 days) after surgery:

- Assessment of AEs (according to CTCAE v5)
- Targeted physical examination
- Vital signs
- ECOG performance status (see Appendix 3)
- ECG
- Pulmonary function test (not mandatory but strongly recommended) (e.g. CPEX/CPET or lung function tests
- FBC and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)
- QoL questionnaires (EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18)
- Participant Health Care Resource Use Questionnaire
- Post-operative complications assessment (using the Clavien-Dindo classification, see Appendix 4)
- Confirmation of commencement of immunotherapy treatment

Research Samples (Adenocarcinoma patients only):

- CfDNA blood sample for exploratory research
- Diagnostic and postoperative histology (refer to section 10 Exploratory Translational Studies)

9.1.10.2 Follow-Up Month 3 (PRIMARY ENDPOINT)

The following assessments are required for the primary endpoint and should be carried out 13 weeks (+/- 7 days) after surgery:

- CT (Thorax, Abdomen and Pelvis), (contrast enhanced, neck optional)
- Assessment of AEs (according to CTCAE v5)
- Targeted physical examination
- Vital signs
- ECOG performance status (see Appendix 3)
- ECG
- Pulmonary function test (not mandatory but strongly recommended) (e.g. CPEX/CPET or lung function tests
- FBC and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)
- QoL questionnaires (EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18)
- Participant Health Care Resource Use Questionnaire
- Post-operative complications assessment (using the Clavien-Dindo classification, see Appendix 4)

Research Samples (Adenocarcinoma patients only):

- CfDNA blood sample for exploratory research

9.1.10.3 Follow-Up Months 6, 9 and 12

The following should be carried out at 6, 9 and 12 months from the date of surgery (+/- 14 days):

- CT and/or PET-CT (Thorax, Abdomen and Pelvis) *(6 and 12 months only),* (contrast enhanced, neck optional)
- Assessment of AEs (according to CTCAE v5)
- ECOG performance status (see Appendix 3) *(6 months only)*
- ECG
- Pulmonary function test (not mandatory but strongly recommended) (e.g. CPEX/CPET or lung function tests
- FBC and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)
- QoL questionnaires (EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18)
- Participant Health Care Resource Use Questionnaire

Research Samples (Adenocarcinoma patients only):

- CfDNA blood sample for exploratory research

9.1.11 Assessments at Completion of SACT treatment

The following should be carried out (28-35 days after administration of last SACT treatment, after disease recurrence, unacceptable toxicity or a year of IO treatment has been administered):

- CT (Thorax, Abdomen and Pelvis), (contrast enhanced, neck optional)
- Assessment of AEs (according to CTCAE v5)
- FBC and differential (haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count)

Research Samples (Adenocarcinoma patients only):

- CfDNA blood sample for exploratory research

9.1.12 Assessments at Disease Recurrence

Patients that have disease recurrence should have the assessments listed below and then come off trial and be followed up according to Sites' local policy:

- CT (Thorax, Abdomen and Pelvis), (contrast enhanced, neck optional), and other imaging as per local policy (if undertaken)
- Assessment of AEs (according to CTCAE v5)
- QoL questionnaires (EORTC QLQ-C30, QLQ-OES18)
- Review of further/additional treatment

Research Samples (Adenocarcinoma patients only):

- CfDNA blood sample for exploratory research

9.2 Observational Sub-Study

Patients that meet the eligibility but decline to participate in the main trial should be invited and given the PIS and ICF for the observational sub-study. No further assessments are required for patients in the observational sub-study. If patients consent, they should be registered to the observational sub-study according to section 7. Sites should complete the following eCRF for patients in the observational sub-study:

- Consent details

The UCL CTC will collect survival data for up to 3 years via data registries (NHS Digital) using the patient's NHS number, date of birth and postcode.

10 EXPLORATORY TRANSLATIONAL STUDIES

10.1 Blood and Tissue Samples

At the time of trial entry, all patients with OAC will be asked for their consent to donate archival tissue blocks and blood samples for exploratory translational research. Patients who decline can still take part in the PROTIEUS study.

Please refer to the PROTIEUS Laboratory Manual for full details on blood and tissue sample collection, storage and shipment.

In summary, all patients with OAC will be invited to provide blood and tissue samples as follows:

- Pre-treatment diagnostic **biopsy tissue** (including one or more formalin-fixed paraffin embedded blocks of biopsy tissue which includes the tumour.

- Blood sample for **germline DNA** (3mls) will be collected in an EDTA tube, pre-treatment (within 21 days prior to starting chemotherapy). *This sample must NOT be collected before randomisation.* Samples must not be frozen or put into the fridge, and must be kept at room temperature and shipped on the same day as collection.

- Blood samples for **cfDNA** (20mls) will be collected in STRECK tubes at the following timepoints:
    - Pre-treatment (within 21 days prior to starting neoadjuvant SACT). *This sample must NOT be collected before randomisation.*
    - Pre-chemoradiation (within 7 days prior to chemoradiation commencing)
    - Completion of CRT assessment
    - Follow-up month 1
    - Follow-up month 3
    - Follow-up month 6
    - Follow-up month 9
    - Follow-up month 12
    - Completion of Adjuvant SACT assessment
    - Disease recurrence

- Blood samples for exploratory translational research must not be collected from patients before they have been randomised to the PROTIEUS trial.
- All blood samples should be kept at room temperature and shipped on the same day they are taken in Royal Mail Safe Boxes (see below for address).

- Surgical **sample tissue** (any residual tumour FFPE tissue blocks and one FFPE tissue block of normal mucosa, for slides).

- FFPE blocks should be shipped once all patients have completed surgery/upon request of the CTC (see below for address).

- All biological samples for exploratory research should be shipped to:

  Victoria Spanswick
  UCL ECMC GCLP Facility
  Ground floor
  UCL Cancer Institute
  Paul O' Gorman Building
  72 Huntley Street
  London
  WC1E 6DD

- Surgical photographs and pseudonymised pathology reports will be uploaded to the UCL XNAT database (refer to section 17.2 Surgical Quality Assurance, and the Surgical QA guidance document).

Please note patients with squamous cell carcinoma are not required to provide blood and tissue samples for exploratory research.

10.2 Collection of Imaging

See imaging manual (separate document). CT/PET/MRI images together with the imaging reports, will be uploaded for 100% patients from each centre from all time-points.

The following sets of images (CT, PET and MRI if available) should be pseudonymised and sent together once each patient has completed 1 year of follow-up/disease recurrence/died, or upon request of the CTC:

- Baseline (pre-randomisation),
- Completion of CRT treatment
- 3 month post-surgery follow-up assessment
- 6 month post-surgery follow-up assessment
- 12 month post-surgery follow-up assessment
- Completion of Adjuvant SACT
- Disease recurrence (if applicable)
- Any additional scans taken due to severe (grade 3) toxicity, (e.g. lung toxicity, heart failure, severe infection) (if applicable)

All scans and reports must be pseudonymised and clearly labelled with the patient's initials and trial number on all scan images, and any other patient identifiers removed/blacked out prior to sending to maintain confidentiality.

10.3 An exploration of whether the pre-treatment OAC transcriptome predicts response to proton-based chemoradiation

Diagnostic formalin fixed paraffin embedded (FFPE) samples from patients randomised in the PROTIEUS trial will be added to a cohort of 190 Oesophageal Cancer patients who underwent neoadjuvant therapy (NAT) followed by surgery from contemporaneous groups. This includes up to 80 samples from Utrecht, the Netherlands, with patients who have undergone carboplatin and paclitaxel neoadjuvant chemoradiotherapy. The remaining patients will come from Southampton and will be matched for neoadjuvant therapy modality. Response to neoadjuvant therapy will be pathologically assessed, as per routine clinical practice, using (Tumour Regression Grade) TRG. Gene expression profiling will be performed with two nuclease protection assay panels (EdgeSeq, HTG – Oncology Biomarker Panel (2568 genes) and Precision Immuno-Oncology Panel (1410 genes)). Sequencing will be performed on the NextSeq500 (Illumina). Differentially expressed genes and pathways will be assessed in “R” to determine the most predictive model of response to NAT. Histological validation will be performed using immuno-fluorescence on the remaining FFPE samples, employing a multispectral overlay technique to examine co-expression of multiple markers and build a comprehensive map of the cellular environment. Furthermore, the results will be combined with bulk and single cell RNA-seq data in the Underwood lab (CRUK Advanced Clinician Scientist Fellowship funded) to understand the transcriptional programmes of OEC.

10.4 Developing Artificial Intelligence models to predict outcomes

1. Multiomic prediction of toxicity probability with patient data available prior to planning stage. There is interest in using normal tissue probability (NTCP) modelling at individual patient level to predict toxicity improvement of proton therapy relative to photon therapy, in order to allocate scarce proton gantry time to those who benefit. Such an approach in a non-trial basis would require substantial resources, in order to dual plan patients for both proton and photon treatments. We will attempt to fit deep learning models to clinical and imaging data available prior to the planning process to see if proton NTCP benefit can be predicted prior to the planning process actually occurring. This would have significant resource benefit implications for future routine NHS streaming of patients to proton or photon based care. Model fittings can be made with all available data (e.g. including genetic data) and also just that data which would typically be available in routine clinical NHS practice. Work on this question could begin as soon as full recruitment has occurred and data release is possible.
2. Prediction of primary endpoint (90-day surgical complications) using full spectrum multiomic data, including clinical, genetic, pathology and imaging data incorporated into hybridised deep learning models. This endpoint can serve as a basis for model development.
3. Prediction of secondary endpoints including disease control, survival, toxicity and quality of life metrics using iterative development and retraining of the developed integrated multiomic deep learning model.

10.5 MRI-based planning and motion mitigation

MRI is increasingly used in oesophageal cancer for target definition and treatment outcome prediction. Oesophageal tumour motion can also be visualised with MRI. In cine-MRI, subsequent 2D images are acquired with a high temporal resolution, which is widely used to study motion patterns in different tumour sites. A mean cranio-caudal (CC) peak-to-peak motion of 13.3 mm with a wide range of 2.7–24.5 mm was found using cine-MRI, in which the mobility of distal tumours was generally larger than that of more proximal tumours.

There is no data regarding MRI guided proton treatment. The changes in tumour anatomical size or function with MRI during proton treatments or the variation in motion when abdominal compression is applied, have not been studied.
Patients receiving PBT will have MR simulation as part of their PBT planning process as per current Standard of Care. The current sequences will include:

- T2 Ax MVXD 4mm
- T2 Cor FS MVXD 4mm
- T1 mDIXON 4mm pre contrast
- T1 mDIXON 4mm post contrast
- 2D OR 3D Cine MR

We plan to introduce MRI into oesophageal proton planning for target delineation, motion visualisation (e.g. peristalsis variation when respiratory motion is dampened).

Aim: To alleviate the risks and uncertainties of accurate proton delivery using MR planning.

Key questions:
1. Which patients are not suitable for motion mitigation using abdominal compression and require other motion mitigation techniques?
2. Can we identify *a-priori* patients that need re-planning due to tumour anatomical changes or other normal tissue variation?

Tasks:
1. Refine MRI sequences to acquire images relating to motion, anatomical changes and function.

10.6 Identifying dose-sensitive cardiac substructures to predict radiation-induced cardiotoxicity

Radiation-induced cardiotoxicity (RIC) is a recognised complication of thoracic radiation, with most understanding historically drawn from studies conducted in lung cancer, breast cancer, and lymphoma [53-58]. However, this treatment complication, which includes

cardiovascular disease, pericardial disease, valvular disease, cardiomyopathy and arrhythmia, is becoming increasingly relevant in oesophageal cancer, particularly as oncological outcomes improve, and avenues of dose escalation and alternative RT modalities are explored. It has also been observed that onset of clinically relevant RIC may be much sooner than initially thought, with heart dose impacting mortality as early as 6 months from treatment [59]. Pertinently, in a group of 479 patients who received photon or proton RT for oesophageal cancer, Wang et al report grade 3 cardiac events at a rate of 18% at 5 years at a median of 7 months following treatment [60], highlighting both the frequency, severity and onset of this treatment complication in this group.

Following oesophagectomy, almost one-fifth of patients suffer with cardiac complications [20]. Though results from the NEOAGIS study, which randomised patients with oesophageal cancer to modern neoCRT or chemotherapy, are yet to be fully reported, there are some data preceding this trial which demonstrate post-operative complications are more severe following Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy [61]. Mechanisms to predict and subsequently prevent RIC are therefore warranted. As radiotherapy techniques become more advanced, it is increasingly accepted that total/mean heart dose may be a suboptimal parameter [53], and that dose received to clinically relevant cardiac substructures such as the coronary arteries, conduction system, pericardium and heart valves may be a more sophisticated measure of risk [53, 62]. Indeed, recently published work by Cai and colleagues demonstrates predictive models for acute coronary syndrome or congestive cardiac failure in patients undergoing RT for oesophageal cancer are more sensitive when incorporating coronary artery substructures versus whole heart variables [62]. However, contouring of the left anterior descending, left circumflex and right coronary arteries is both time consuming and user dependant, even with the aid of contour guidelines [63]. Furthermore, other important structures such as the conduction system are not visible on CT [62], and anatomical surrogates are difficult to identify.
This study will evaluate a voxel-based analysis (VBA) for patients treated with both photon and PBT. This approach has previously correlated dose to the base of the heart with early mortality in patients with lung cancer in multiple patient populations [59, 64, 65]. This region is clinically significant, as it is the location of the proximal coronary arteries as well as the Sino Atrial node. This region is now the focus of an ongoing prospective study, RAPID-RT [66]. Voxel based analysis follows the pre-defined methodological steps:

1. Spatial normalisation of individual anatomies to a common reference anatomy;
2. Statistical inference on the spatial signature of dose response.

Spatial normalisation will be performed to the common reference anatomy, representative of the patient population. Multiple reference anatomies will be utilised to ensure robustness to this underlying assumption. Spatial normalisation will be performed by 1. an affine registration of each patient to the reference patient; 2. non-rigid registration to the reference patients; registration will focus on the lung and heart volumes with bones removed by thresholding the image to mitigate potential uncertainties with sliding tissue interfaces between ribs and lung tissue.
Registration quality will be assessed by 1. visual inspection of the registrations and 2. quantitative assessment of the alignment of the heart using the available clinical contours. The variation of the centre of mass of the heart contour will be calculated. This process will be repeated using an in-house AI auto-segmentation model. Registration uncertainty will be accounted for in the analysis by blurring the dose for each patient with a 3D-

Gaussian width set to the standard deviation of the heart centre of mass coordinate in each cardinal direction.
Statistical inference will be performed per-voxel. To correct for multiple comparisons (i.e., it is likely that the null hypothesis was incorrectly rejected for some voxels, type I errors) permutation testing will be used to define the significance threshold for the statistical test. This will follow the process defined above and described by Palma *et al*. (Physica Medica, 2019).

Two statistical approaches will be implemented in this project.

1. Univariable 2-sample t-test, with binary endpoints defined at set times post treatment (6-months, 12- months, 18-months, 24-months). A 95th percentile significance level will be defined from permutation testing. Dose from this region will be extracted and analysed within a multi-variable Cox regression survival model.
2. Univariable and multivariable Cox-regression per voxel allowing a time-to-event (Green et al. Frontiers Oncology, 2020). Overall survival will be analysed as the endpoint.

Aims: To identify dose sensitive regions within the heart that correlate with mortality and/or cardiac toxicity in the setting of NA-IMRT and PBT for oesophageal cancer.

10.7 Developing and evaluation of image analysis tools to support radiotherapy planning, delivery, and follow-up

The detailed three-dimensional imaging, dosimetry data and outcome data collected will be valuable in studies focused at developing and evaluating novel image analysis algorithms and tools tailored to radiation oncology. Key areas of application that the algorithms may be developed are: radiotherapy treatment planning, risk assessment, quality assurance workflows, image-guidance protocols, treatment verification and adaptation workflows, and treatment follow-up. The goal is to develop and evaluate emerging novel image analysis tools that improve the accuracy, efficacy, and efficiency of radiotherapy planning, delivery, and follow-up workflows. The algorithms and tools will be developed for image analysis tasks such as image segmentation, registration, medical image synthesis and computational simulation. For example, we will look into developing novel image analysis methods to objectively quantify normal tissue damage on routine CT imaging to measure post-RT radiological changes in the heart and lungs [67]. These radiological endpoints may allow to identify potential imaging differences between subjects treated with proton versus photon treatments and contribute to better understanding the spatial-varying relative radiobiological effectiveness of protons and its impact in normal tissue toxicity (which is still widely discussed in the community). Radiological endpoints can also link to predictive models of radiation-induced toxicity, using conventional, dose-volume histogram based normal tissue complication probability models and more advanced three-dimensional, voxel-based techniques to model toxicity. The on-board imaging information, coupled with image analysis algorithms,[68] will allow studies to describe how anatomical change and setup errors affect photon versus proton plans, and to develop computational methods for robust planning and to accumulate delivered dose in this cohort of patients for follow-up dose-response studies, allowing to

understand and mitigate for the clinical impact of the increased physical uncertainties in proton dose delivery.

10.8 Predictive and prognostic measures of body composition on clinical outcomes

The same imaging datasets will be used to analyse body composition. Nearly 80% of oesophageal cancer patients are malnourished at diagnosis [69], the most of any cancer site [70, 71], with dysphagia experienced by many patients [72]. Poor nutritional status leads to weight loss, muscle wasting and decreased functional status. All of which are known prognostic factors across cancer populations where they are associated with decreased survival and increased treatment toxicities [73-75]. In particular, skeletal muscle health, evaluated by extracting cross-sectional muscle area from CT scans, provides insight into patient fitness, offering independent information compared to performance status and BMI. Typically, muscle area is extracted by segmenting the muscle compartment at the L3 vertebral level and adjusting for patient height squared. However, L3 is not always visible in routine CT imaging of oesophageal cancer patients. To address this, we have developed an in-house toolkit capable of automatically segmenting skeletal muscle across vertebral levels.
This toolkit was used to evaluate muscle mass at the T12 vertebral level in 135 patients with oesophageal cancers treated with definitive chemoradiotherapy at a single centre [74]. This work similarly confirmed that muscle mass was an independent prognostic factor, providing additional information compared to BMI and performance status. Patients with both low muscle mass and low BMI were most at risk of mortality. In addition, this work showed that patients with low muscle mass were more likely to develop lymphopenia post-CRT, highlighting the association between immune function and skeletal muscle health.

The proposed analysis will take advantage of CT imaging acquired at multiple time-points throughout the treatment pathway (as per the defined schedule of events). The skeletal muscle compartment will be automatically segmented at the T12 vertebral level. Muscle characteristics including muscle area and muscle attenuation will be extracted. Decreased muscle health often leads to increased intra-muscular adipose tissue (myosteatosis). Therefore, measures of fat infiltration will also be extracted. By incorporating measures of immune function (neutrophils, lymphocytes and platelets), collected from blood serum samples which are already being collected as SOC, at multiple timepoints, this will enable a longitudinal analysis comparing the effects of different treatments (photons vs protons) on muscle health and immune health. Per-patient trajectories of muscle and immune characteristics will be formed, and correlations calculated. Subsequently trajectories will be stratified on treatment regimen, where differences between groups will be identifiable. Finally, measurements (both baseline and trajectories) will be correlated with treatment outcomes, enabling the identification of characteristic changes to body composition and blood markers most associated with mortality, treatment toxicities, quality-of-life, and subsequent tolerability of adjuvant immunotherapy.
Results from this work will improve the management of patients with oesophageal cancer by improving patient stratification based utilising muscle mass as a prognostic biomarker.

Our hypothesis is that muscle mass at T12 will also act a predictive biomarker for clinical outcomes. We will seek to evaluate this hypothesis by correlating the muscle mass at T12 with differences in clinical outcomes between patients treated with PBT vs. photons. If a difference is present, we will seek to further determine if this biomarker may aid patient selection for PBT and adjuvant immunotherapy. Furthermore, this will enable future studies to identify pharmaceutical and physical activity interventions capable of protecting musculoskeletal health and immune health throughout treatment, ultimately improving quality-of-life and survival.

Aim: validation of the prognostic and predictive impact of muscle mass on clinical outcomes in patients receiving neoadjuvant chemoradiation in oesophageal cancer. Identify correlations with rates of lymphopenia and subsequent tolerability of adjuvant immunotherapy.

11 DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites using an electronic case report form (eCRF) created and maintained by UCL CTC. Data must be accurately transcribed on to trial eCRFs and must be verifiable from source data at site. Examples of source documents are hospital records, which include patient's medical notes, laboratory and other clinical reports.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending, to maintain confidentiality. Refer to section 14 (Trial Monitoring and Oversight) for further details of centralised monitoring of source documentation.

Please note that, for this trial, patients must consent to their date of birth, postcode and NHS number being supplied to UCL CTC. This is:

- for flagging with data registries (NHS Digital)
- to assist with follow-up via GPs

Patient questionnaires (EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18, Participant Health Care Resource Use Questionnaire (modified CSRI)) for this trial will be completed by patients in a module of OC called participate. Patients will be asked to consent to providing their contact details (name, email and mobile telephone number) in order to receive the link via email or text to complete these online.

11.1 Entering data into the eCRF

The eCRF must be completed by site staff who have been appropriately trained, are listed on the site staff delegation log and authorised by the PI to perform this duty. Each authorised staff member will be issued with their own unique login details for the eCRF by UCL CTC, and a list of current users at each site will be maintained by UCL CTC. Site staff must never share their login details with other staff as the eCRF audit trail will record all entries/changes made by each user. The PI is responsible for the accuracy of all data reported in the eCRF.

The use of abbreviations and acronyms must be avoided.

11.2 Corrections to eCRF Forms

Where necessary, corrections can be made by site staff to data on the eCRF, as long as the eCRF has not been locked/frozen by UCL CTC. The eCRF audit trail will record the original data, the change made, the user making the change and the date and time. Site staff should contact UCL CTC if changes need to be made to a locked/frozen eCRF.

11.3 Missing Data

To avoid the need for unnecessary data queries, fields should not be left blank on the eCRF. If data is unavailable, please refer to the eCRF Completion Guidance for information on how to indicate that data is "Not Done", Not Applicable", "Not Available" or "Not Known" (only use if every effort has been made to obtain the data).

11.4 Timelines for Data Entry

The relevant eCRF forms must be completed as soon as possible after a patient's visit.

Sites who persistently do not enter data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and this may trigger a monitoring visit. See section 14 (Trial Monitoring and Oversight) for details.

11.5 Data Queries

Data entered onto the eCRF will be subject to some basic checks at the time of entry, and any discrepancies will be flagged to the user in the form of a warning. The data can be corrected immediately, or where this is not possible, the warning can be saved and the data amended at a later stage.

Further data review will be carried out at UCL CTC and queries raised where necessary. Further guidance on the process for handling data queries can be found in the eCRF Completion Guidance.

There may be times when data queries require a rapid response e.g. if an urgent safety issue is detected or an Independent Data Monitoring Committee (IDMC) meeting is due. UCL CTC will contact sites if this is the case and provide as much notice as possible.

12 SAFETY REPORTING

12.1 Definitions

The following definitions have been adapted from the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and subsequent amendments, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with research procedures. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with a research procedure(s), whether or not related to that procedure(s). See section 12.2.1 for AE reporting procedures.

Adverse Event of Importance for PROTIEUS (AEIP)

An AE that is of scientific interest to the Trial Management Group. The AEs of importance for PROTIEUS (AEIP) are listed in section 12.2.2.

Serious Adverse Event (SAE)

An adverse event that:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which 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 prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that 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 other outcomes listed above)

See section 12.2.3 for SAE reporting procedures.

Related and Unexpected Serious Adverse Event

An adverse event that meets all the following criteria:

- **Serious** – meets one or more of the serious criteria, listed under the definition of SAE above
- **Related** to the study (i.e. resulted from the administration of any of the research procedures)

- **Unexpected** (i.e. not listed in the protocol (appendix 2) as an expected occurrence)

See section 12.2.4 for reporting procedures for these events.

Overdose, Research procedure error, or Occupational exposure

Refer to section 8.5 for details on reporting of these events.

12.2 Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 should be used. This is available online at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

Severity grade

Severity grade of each adverse event must be determined by using CTCAE v5.0.

Causality

The relationship between the research procedures and adverse events will be assessed.

For AEs (including SAEs) the local PI or designee will assess whether the event is causally related to treatment.

For SAEs a review will also be carried out by the Sponsor's delegate.

Causal relationship to each research procedure must be determined as follows:

- Related (reasonable possibility) to a research procedure
- Not related (no reasonable possibility) to a research procedure

UCL CTC will consider events evaluated as related to be related adverse events.

12.2.1 Reporting of Adverse Events (AEs)

All adverse events that occur between the start of chemoradiotherapy treatment and 1 year after surgery must be recorded in the patient medical notes and the trial eCRFs.

All adverse events that are adverse events of importance for PROTIEUS (AEIP) that occur between randomisation and 1 year after surgery must be recorded in the patient medical notes and the trial CRFs (see section 12.2.2).

Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the SAE report in the trial-specific OpenClinica database. Also see section 12.2.3 (Reporting of Serious Adverse Events (SAEs).

Pre-existing conditions (i.e. conditions present before starting chemotherapy treatment) do not qualify as adverse events unless they worsen or recur (i.e. improves/resolves and then worsens/reappears again).
e.g. an AE could be an exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition (worsening of the event). Another example of an AE is when a pre-existing condition improves during the trial (e.g. from grade 3 to grade 1) and then it worsens again (e.g. from grade 1 to grade 2), even if the event is of severity equal or lower to the original condition (improvement and recurrence of the event).
NB: The disease under study and its anticipated day-to-day fluctuations would not be an AE.

Exemptions from AE Reporting

For this trial, the following events are exempt from requiring reporting on the AE Report eCRFs:

- Any CTCAE v5 grade 1 or 2 events ***except***
    - *AEs of importance for PROTIEUS (AEIP) (see section 12.2.2)*

Note: SAEs of any grade should be reported on the OpenClinica SAE report, except those that are exempt (see section 12.2.3)

12.2.2 Reporting of Adverse Events of Importance for PROTIEUS (AEIP)

The following adverse events of importance for PROTIEUS (AEIP) must be reported between randomisation and 1 year after surgery. They must be reported on the Adverse Events eCRF on the PROTIEUS OpenClinica database if they occur at any grade and regardless of their seriousness. These events **do not** require expedited reporting (unless they meet the criteria for an SAE), and should just be reported on the OpenClinica database according to the timelines in section 11.4 (Timelines for Data Entry). Severity grade of each adverse event must be determined by using CTCAE v5.0.

System Organ Class	Event term
Cardiac Disorders	• Acute coronary syndrome: myocardial infarction • Cardiac Toxicity • Cardiac Conduction disorder/atrial fibrillation, atrioventricular block, other: please specify • Heart failure • Pericarditis/ pericardial effusion
Gastrointestinal disorders	• Dysphagia • Gastrointestinal Fistula/perforation • Gastritis/ Gastric ulceration • Oesophagitis/oesophageal ulceration

System Organ Class	Event term
	• Oesophageal perforation (with/without mediastinitis) • Oesophageal stenosis • Tracheo-oesophageal fistula • Upper Gastrointestinal Haemorrhage
Investigations Blood and lymphatic system disorders	• Lymphocyte count
Respiratory, thoracic and mediastinal disorders	• Aspiration • Atelectasis • Pleural effusion • Pneumonitis • Pulmonary fibrosis • Pneumonia • Pneumothorax • Respiratory failure

12.2.3 Reporting of Serious Adverse Events (SAEs)

All SAEs that occur between randomisation and 30 calendar days post-surgery must be reported to UCL CTC using the SAE Report eCRF in the trial-specific OpenClinica database within **24 hours** of observing or learning of the event, followed by an email sent to the trial mailbox to notify an SAE has been reported in OpenClinica.

All sections on the SAE Report eCRF must be completed. If the event is **not being reported to UCL CTC within 24 hours**, the circumstances that led to this delay must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE Report. However, the events must be recorded in the relevant sections of the trial eCRFs:

- Events related to chemotherapy, photon based radiotherapy, or immunotherapy**, (note: events related to proton-beam radiotherapy and surgery are not exempt and must be reported as an SAE).**
- Events that occur more than **30 calendar days** post-surgery. Note: this does not include pregnancy related events (see section 12.4)
- Disease recurrence (including disease-related deaths)

Please note that hospitalisation for elective treatment, palliative care, socio-economic or logistic reasons does not qualify as an SAE.

SAE Report eCRFs must be completed on the trial OpenClinica Database within 24 hours of becoming aware of the event using the SAE report CRF in the OpenClinica database and a notification email sent to

Email: ctc.PROTIEUS@ucl.ac.uk

OpenClinica Systems Failure

In the unlikely event of OpenClinica systems failure, the following information should be reported to UCL CTC by sending an email to ctc.PROTIEUS@ucl.ac.uk

- Trial name
- Patient's trial number
- Reporter's name
- SAE details (event term, grade, seriousness criteria)
- Randomised arm
- Assessment of causal relationship

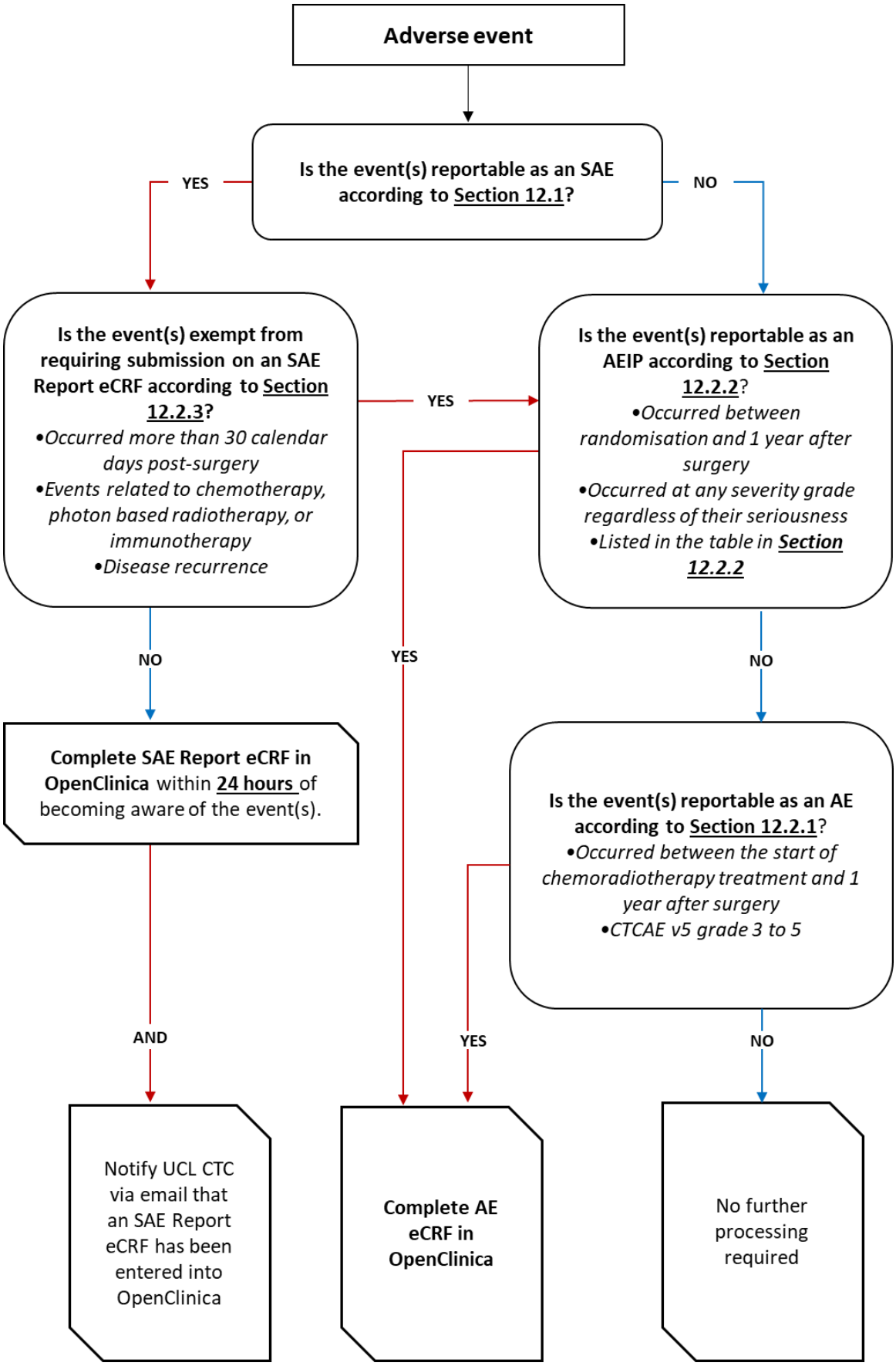
An SAE report eCRF must be promptly submitted in OpenClinica, once the system is operational.

SAE Follow-Up Reports

UCL CTC will follow up all SAE until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC promptly. If an event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to the delay must be detailed in the SAE Report to avoid unnecessary queries.

SAE, AEIP and AE Reporting Flowchart



SAE Processing at UCL CTC

On receipt of an SAE Report on OpenClinica, UCL CTC will check for completeness, accuracy and consistency. UCL CTC will evaluate expectedness, to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events in protocol appendix 2. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate (e.g. a clinical member of the TMG), will be consulted for their opinion.

12.2.4 Related and Unexpected Serious Adverse Events

If the event is evaluated as a Related and Unexpected Serious Adverse Event, UCL CTC will submit a report to the REC within the required timeline.

Informing Sites of Related and Unexpected Serious Adverse Events

UCL CTC will inform sites of any related and unexpected SAEs that occur on the trial. Sites will receive a quarterly line-listing which must be processed according to local requirements.

12.3 Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

The IDMC will review the following trial safety data:

- Disease-related events (exempt from SAE reporting as per section 12.2.3) according to treatment allocation to identify whether disease-related events appear to be enhanced by the research procedures;
- Line listing of related adverse events and adverse events due to research procedures to identify new adverse reactions;

The IDMC and TMG will review trial safety data to identify:

- Trial related events or incidents that may lead to changes to the trial documents.

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary, the issue will be referred to the IDMC.

12.4 Pregnancy

Reporting Period

For any pregnancy exposure to research procedures, the site must submit a Pregnancy Report to UCL CTC by completing the eCRF on OpenClinica within **24 hours of learning of its occurrence**.

A pregnancy exposure to research procedures includes pregnancy in a trial patient in the PBT arm only, occurring from start of treatment until six months after last PBT administration.

The site must request consent from the pregnant trial patient to report information regarding a pregnancy using the trial-specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients (optional).

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

All reportable pregnancies must be reported by completing the Pregnancy Report eCRF on OpenClinica within 24 hours of becoming aware of the pregnancy

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up during pregnancy and for up to 6 weeks after the end of the pregnancy (or later if there are ongoing issues) to collect information on any ante- and post-natal problems for both mother and child. If significant new information is received, follow-up Pregnancy Reports must be submitted on OpenClinica to UCL CTC within **24 hours** of learning of the new information. In case of adverse outcome to the pregnancy reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported on the SAE Report eCRF on OpenClinica, according to SAE reporting procedures. Refer to section 12.2.3 (Reporting of Serious Adverse Events (SAEs)) for details.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the REC if the pregnancy outcome meets the definition of a related and unexpected SAE. Refer to section 12.2.4 (Related and Unexpected Serious Adverse Events) for details.

13 INCIDENT REPORTING AND SERIOUS BREACHES

13.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. When an incident report is requested by UCL CTC this should be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed. Where an equivalent document is being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers redacted prior to sending, to maintain confidentiality.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2 Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with the principles and conditions of GCP and/or the protocol, including failure to report SAEs occurring on study within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the REC within 7 calendar days of becoming aware of the breach.

14 TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Where permitted by site policy, remote access to source data/documents may also be provided by participating sites for remote monitoring by UCL CTC or its representatives.

Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. UCL CTC or its representatives will conduct all monitoring in compliance with the participant consent, site policy and data protection requirements.

UCL CTC will determine the appropriate level and nature of monitoring required, based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

Details of monitoring activities will be included in the trial monitoring plan and conveyed to sites during initiation. The trial monitoring plan will be kept under review during the trial and updated information provided to sites as necessary.

14.1 Centralised Monitoring

UCL CTC performs centralised monitoring, which requires the submission of documents by sites to UCL CTC for review, including but not limited to:

- Delegation Log
- Screening Log
- Samples Log

Expectations for document submission will be explained during site initiation and UCL CTC or its representatives will send emails to sites requesting the documents when required.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File at the frequency determined for the trial. Checklists detailing the current version/date of version-controlled documents will be provided by UCL CTC for this purpose.

On-site/remote monitoring visits may be scheduled following UCL CTC review and/or where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

On-site Monitoring

Sites will be sent an email in advance outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote Monitoring

UCL CTC defines remote monitoring as monitoring activities conducted at a location remote from the research site which replicate some on-site activities e.g source data review. Remote monitoring may be conducted in response to exceptional circumstances preventing access to participating sites (e.g. global pandemic) or conducted routinely. Details of remote monitoring will be agreed with participating sites, conducted in accordance with site policy and documented in the monitoring plan.

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing remote monitoring.

Remote monitoring will be conducted by UCL CTC or its representatives via a device with adequate security. Patient confidentiality will be maintained at all times, and monitoring activities will be conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties. Also refer to section 11 Data Management and Data Handling Guidelines for details of how source documentation may be submitted to UCL CTC.

Monitoring Follow up

Following on-site/remote monitoring, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

14.2 Escalation of monitoring issues

Where monitoring indicates that a patient may have been placed at risk, the matter will be raised urgently with site staff and escalated as appropriate.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches) for details.

14.3 Oversight Committees

14.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and PROTIEUS trial staff from UCL CTC (see page 1). The TMG will be responsible for overseeing the trial. The group will meet regularly, at least twice a year, and will send updates to PIs (via newsletters or at Investigator meetings).

The TMG will review substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

A TMG charter, which outlines the responsibilities for the PROTIEUS trial, must be signed by all members of the committee.

14.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

The PROTIEUS trial is reviewed by an established UCL CTC TSC that has oversight of several trials. All members have signed a TSC charter.

14.3.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held once a year to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

An IDMC charter, which outlines the responsibilities for the PROTIEUS trial, must be signed by all members of the committee before the first meeting is held.

14.3.4 Role of UCL CTC

UCL CTC, on behalf on the sponsor, will be responsible for the day-to-day coordination and management of the trial and the UCL CTC Director will act as custodian of the data generated in the trial (on behalf of UCL).

15 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples and imaging, follow-up, and data collection.

15.1 Patients who do not start Trial Treatment

If a patient does not start treatment the reasons for this must be recorded in the patient's medical notes and on the relevant Case Report Form(s). Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision
- No longer eligible

If a patient does not start treatment, then the patient should be withdrawn from the trial. Data collected about the patient so far will be used in the trial analysis, where appropriate. Biological samples collected and imaging may still be used unless the patient explicitly withdraws consent to this.

15.2 Discontinuation of Trial Treatment

A patient may discontinue trial treatment if the treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's medical notes and on the relevant Case Report Form(s). Reasons for discontinuing treatment may include:

- Disease recurrence whilst on trial treatment
- Unacceptable toxicity
- Intercurrent illness that prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition that justifies the discontinuation of trial treatment in the site investigator's opinion
- Non-compliance with the trial treatment and/or procedures
- If a female patient becomes pregnant or male/female fails to use adequate birth control (for patients of childbearing potential)

In these cases, patients will remain on the trial for the purposes of follow-up and will be included in appropriate data analysis, unless they explicitly withdraw consent to this.

If a patient expresses their wish to discontinue trial treatment, sites should explain the importance of remaining on trial follow-up, or of at least allowing routine follow-up data and data already collected to be used for trial purposes. If the patient gives a reason for wishing to discontinue trial treatment this should be recorded.

The following CRFs should be submitted if a patient discontinues trial treatment early:

- Completion of Treatment/Treatment Summary/End of Treatment Form
- Treatment forms for all cycles of treatment received

- Adverse event form(s) for all cycles of treatment received

Thereafter, unless the patient has withdrawn consent for data collection, the following CRFs should continue to be submitted:

- SAE reports
- Adverse event forms
- Follow up forms
- Disease recurrence form
- PROMs (EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18, Participant Health Care Resource Use Questionnaire (modified CSRI))

15.3 Withdrawal of Consent

If a patient withdraws consent for any aspect of the study, UCL CTC should be notified and the Change of Status form should be completed and submitted to UCL CTC.

15.3.1 Withdrawal of consent for follow up

If a patient withdraws consent for trial follow up, but is happy to continue with future data collection from hospital medical notes/NHS Digital

- They will remain on trial for follow up
- The patient will no longer have trial-specific visits and assessments. Follow up forms should be completed based on the routine visit nearest the due date for the follow up form
- The following CRFs/data must be submitted at time of withdrawal:
    - Change of Status form
    - All CRFs up to and including the date of withdrawal of consent
- Thereafter, the site should report AEs/SAEs as per section 12.2 and follow up forms, including notifications of recurrence, death and second malignancy.

15.3.2 Withdrawal of consent for data collection

If a patient **explicitly** states they do not wish to contribute further data to the trial their decision must be respected. The following CRFs must be submitted at the time of withdrawal of consent:

- Change of Status Form
- All CRFs up to and including the date of withdrawal of consent

Thereafter, no further data should be submitted, with the exception of SAE reports as per section 12.2 (due to the regulatory requirement for oversight of patient safety).

15.3.3 Withdrawal of consent for use of samples

If a patient withdraws consent for the use of some, or all, of their samples in the trial, or for future research, this should be reported on the Change of Status form. Unless the patient has also withdrawn from trial treatment/follow up, management and data collection should continue as per protocol.

15.4 Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for the patient to be followed up via the patient's GP. Details of participating trial sites can be obtained from the UCL CTC trial team, who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer to another participating site, the registering site remains responsible for submission of CRFs.

If a patient is lost to follow-up, every effort should be made to contact the patient's GP to obtain information on the patient's status.

Patients who are lost to follow up will be tracked by UCL CTC via NHS Digital.

At the time of loss to follow up, the following CRFs should be submitted:

- Change of Status form
- All CRFs due up to and including the date of loss to follow up

If contact is re-established with the patient, further follow up forms should be sent, including notifications of disease recurrence. A death form should also be submitted if the site becomes aware that the patient has died.

Prior to primary analysis and presentation/publication of the primary endpoint data, UCL CTC will ask sites to attempt to re-establish contact with patients who were lost to follow up and/or check hospital records for evidence of when the patient was last known to be alive and evidence of death, disease recurrence or second malignancies.

15.5 Loss of Capacity

Capacity refers to the everyday ability that individuals possess to make decisions or to take actions that affect them. A person lacks capacity if he or she is unable to make or communicate a decision about a particular matter because of an impairment of, or a disturbance in, the mind or the brain. This may be the result of a variety of conditions, including:

- dementia
- mental illness
- learning disability
- brain damage
- intoxication
- any other condition causing confusion, drowsiness or loss of consciousness (e.g. concussion, stroke, heart attack, epileptic fit, serious accident, delirium).

Patients who lose capacity during the trial would be withdrawn from the trial and treated according to local procedures. Any pseudonymised data and samples that were already collected for the trial, would be retained and used in the trial and other studies. No further data or samples would be collected.

16 TRIAL CLOSURE

16.1 End of Trial

For regulatory purposes the end of the trial will be 24 months after the last patient has completed their final follow up. At this point the 'declaration of end of trial' form will be submitted to Ethics Committee, as required, and sites notified.

UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3 Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.3.2 (Trial Steering Committee (TSC) and 14.3.3 (Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4 Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the site agreement.

17 QUALITY ASSURANCE

17.1 Radiotherapy Quality Assurance

A comprehensive quality assurance programme is in place for PROTIEUS. In brief: there will be a pre-accrual and on-trial component to the QA process. Centre-specific pre-accrual QA will be determined according to previous participation in UK oesophagus trials, in line with the National Radiotherapy Trials Quality Assurance (RTTQA) group move towards streamlining. Pre-accrual QA will consist of outlining a benchmark case and creating a treatment plan. On-trial reviews will be a combination of prospective and timely retrospective reviews following clearly defined criteria. To treat a patient with the outlining clinician, the treatment technique and the process documentation must be approved by the national RTTQA team. We will align with international colleagues as part of a proton working group within the Global Harmonisation Group. The selected teams already have expertise in delivering high quality oesophageal specific radiotherapy as part of the current and previous oesophageal studies [76]. This proposal has been discussed with the RTTQA group. UCLH and The Christie PBT centres have an identical proton QA process.

17.2 Surgical Quality Assurance

(See separate Surgical QA document). This will be led by Dr Blencowe, who has extensive experience of developing QA protocols for surgical studies. She led the QA programme in the NIHR-HTA ROMIO study (HTA -14/140/78), which established parameters for oesophagectomy in multicentre trials. Adherence to these standards [77] will be monitored in case report forms and by digital photographs of key operative phases (abdominal and thoracic lymphadenectomy; hiatal dissection) and pseudonymised pathology reports which will be uploaded to the UCL XNAT database (see imaging manual).

18 STATISTICS AND HEALTH ECONOMICS

18.1 Sample Size Calculation

We assume that the grade ≥3 post-operative complication rate with photon RT is 44% (the lowest observed rate from previous prospective clinical trials [78]).

We expect that PBT would reduce this by a third, i.e. to 29% (reported in Baumann [36] of which 150 gastro-oesophageal proton).

To detect this difference (44% vs 29%) requires 116 patients (58 per arm) with 80% power, and one-sided statistical significance of 20%.

Anticipating a 10% dropout rate across both arms, we intend to recruit up to 130 patients with adenocarcinoma.

Because of the concern over having a heterogenous cohort with mixed histologies (with the potential to dilute treatment effects and the translational components), there will be an additional cohort of 20 patients per arm with squamous cell carcinoma. (Overall this represents 23% of patients recruited in the PROTIEUS trial; CROSS [8] study has 23% OSCC and CheckMate-577 [16] has 29% OSCC).

This means that we can analyse all patients together (170 in total, with power higher than 80%), but also be powered for the adenocarcinoma group alone.

18.2 Statistical Analysis

18.2.1 Analysis of main endpoint

Endpoint	Definition	Analysis
Severe post-operative complications at 90 days post-surgery	Post-operative complications (POC) are defined as grade ≥3 according to the Clavien-Dindo criteria and CTCAE v5.0, as included in the Esophageal Consensus.	The frequency and percentage of patients who experienced POC prior to or at 90 days post-surgery will be reported by treatment arm. The difference in proportions test will be used to compare treatment groups. The difference in proportions along with 80% CI, 95% CI and p-value will be reported. To adjust for the randomisation stratification factors (T stage and N stage), logistic regression will also be performed and treatment odds ratio for the risk of POC will be reported along with 80% CI, 95% CI and p-value. Logistic regression will be also performed to adjust for relevant baseline covariates.

Endpoint	Definition	Analysis
		The analysis will be performed amongst patients who underwent surgery. Death due to any cause within 90 days post-surgery will be considered POC. The worst severity grade of each type of POC will be computed per patient and reported.

18.2.2 Analysis of secondary endpoints and secondary analyses

Endpoint	Definition	Analysis
Pathologic Complete response rate	Pathological complete response is defined as a surgical specimen without evidence of cancer in the primary tumour or lymph nodes.	The frequency and percentage of patients with pCR will be presented. Percentage of Complete responders will be calculated over the total of patients who underwent surgery and had pathological specimen. Patients who died before surgery will be classified as non-responders.
Clear margin resection (R0) rate	Clear margin resection (R0) is defined as carcinoma more than 1 mm from the margin	The frequency and percentage of patients achieving R0 will be presented. Percentage of patients achieving R0 will be calculated over the total of patients who underwent surgery and had pathological specimen. Patients who died before surgery will be classified as non-responders.
Disease-free survival	Disease-free survival is measured from time from randomisation until disease recurrence, progression or death, whichever occurs first. Patients for whom a DFS event is not reported will be censored at the date last seen alive.	The disease free-survival rate at 6, 12, 24 months will be reported using the Kaplan Meier method along with 95% CI by treatment arm. The median DFS time will also be reported with 95% CI by arm. DFS curves will be depicted by arm using the Kaplan Meier plot. Cox regression will be used to assess the effect of treatment on DFS, reporting hazard ratios, 95% CIs, and p-values.
Overall survival	Overall survival is measured from the date of randomisation to the date of death from any cause. Patients for whom death is not reported will be censored at the date last seen alive.	The overall survival rate at 6, 12 and 24 months will be reported using the Kaplan Meier method along with 95% CI by treatment arm. The median overall survival time will also be reported with 95% CI by treatment arm.

Endpoint	Definition	Analysis
		Overall survival curve will be depicted by arm using a Kaplan Meier plot. Cox regression will be used to assess the effect of treatment on overall survival, reporting hazard ratios, 95% CIs, and p-values.
Pre-surgery toxicity, and 30-day and 90-day post-operative mortality and treatment rates of completion	Rate of death due to toxicity prior to surgery is defined as the percentage of patients who died before surgery due to a cause related to research procedures. Rate of post-operative death at 30 and 90 days is defined as the percentage of patients who died due to surgical complications within 30 or 90 days from surgery, respectively.	The frequency and percentage of patients who died prior to surgery, within 30 days post-surgery and within 90 days post-surgery will be reported in a descriptive manner by treatment arm.
Suitability to receive adjuvant SACT	The suitability to receive adjuvant SACT is defined as the proportion of all randomised patients who underwent surgery and received adjuvant SACT.	The frequency and proportion of patients who received adjuvant SACT will be presented for each group. A test of difference in proportions will be performed.
Time from surgery to commencement of adjuvant SACT	This endpoint is measured as the duration in days from surgery to the initiation of adjuvant SACT	It will be analysed using descriptive analyses such as medians and ranges. They will be compared between treatment groups.
Rate of completion of adjuvant SACT	Completion of adjuvant SACT is defined as the percentage of patients who started adjuvant SACT and received 12 months of adjuvant treatment.	The frequency and proportion of patients who completed adjuvant SACT will be presented by arm. A test of difference in proportions will be performed amongst patients who started adjuvant SACT.
Grade 4 Lymphopenia	Lymphopenia will be graded according to CTCAE v5.0 (lymphocyte count decreased).	The frequency and proportion of individuals experiencing a CTCAE v5 Grade 4 lymphopenia event (lymphocyte count decreased) will be presented descriptively by treatment group. Only patients who started CRT treatment will be included in the analysis.
Time from completion of neoadjuvant chemoradiotherapy to surgery	The time from the completion of neoadjuvant chemoradiotherapy to surgery will be measured. The failure event (not receiving surgery) can be fulfilled by progression, death, or other	A competing-risks regression model according to the method of Fine and Gray [79] will be performed. Competing factors include disease progression, death, and other reasons for failure to receive surgery. The sub-hazard

Endpoint	Definition	Analysis
	reasons for failure to receive surgery.	ratios from the competing risk analysis will be reported alongside the 95% CIs and adjusted for relevant baseline covariates.
Number of patients who complete their radiotherapy regimen and reasons for non-completion.	The radiotherapy regimen is defined as completed when a patient has been administered the total planned dosage of 40.05Gy given in 15 fractions over 3 weeks, with 5 fractions administered weekly, using either proton or photon radiotherapy.	The frequency and percentage of patients who completed their radiotherapy treatment will be reported in a descriptive manner by treatment arm. Percentages will be computed over the total of patients who started treatment. Reasons for treatment discontinuation will be summarised in terms of frequency and percentages of patients by treatment arm.
Disease recurrence mapping including oligometastatic disease	The types of disease recurrence will be defined as: oligometastatic disease, localised disease, locoregional disease, widespread (or polymetastatic) disease, micrometastatic disease, Other	The number and percentages of different types of disease recurrences (including oligometastatic disease) will be reported by treatment arms. Only descriptive analysis will be presented.
Total toxicity burden (TTB):	TTB is defined as a severity-weighted sum over the different toxicities that may occur up to 12 months from CRT.	The TTB will be computed for each patient and standardised by time. The mean (SD) and median (range) time-standardised TTB will be reported by arm. Two independent sample T-test or a non-parametric alternative will be performed to compare treatment groups in terms of the time-standardised TTB. Refer to Appendix 6 for the list of AEs, severity and corresponding weights and reference.
Change in quality of life over time	Assessment will be performed at a baseline and key follow-up time points, using EQ-5D-5L, EORTC QLQ-C30, QLQ-OES18, and qualitative study of patient experience with proton beam therapy	The median and range will be reported at each time point for each QoL measure by arm. The results will be presented in a descriptive manner in tables and plots.
Frequency of adverse events	Adverse events will be classified and graded according to CTCAE v5.0. The worst severity grade for each type of toxicity will be calculated for each patient.	The number and percentage of patients experiencing any adverse event will also be reported by severity. Pre-surgery toxicity will be reported by the type of event and by severity within each

Endpoint	Definition	Analysis
		treatment group. Only patients who started research procedures will be included in the analysis. Adverse events will be presented separately in a descriptive way for each arm. Adverse events grade 3-5 will reported for each type of event and by arm in a descriptive manner using frequencies and percentages. Adverse events of importance for PROTIEUS will be reported for each type of event, by arm and by severity (grade 1-2 and 3+) in a descriptive manner using frequencies and percentages.

18.3 Health Economics

For the primary health economic analysis, the mean incremental cost per quality-adjusted-life-year (QALY) gained on using proton-based chemoradiotherapy compared to control arm (photon based chemoradiotherapy), will be calculated from the perspective of the NHS and Personal Social Services (as preferred by the National Institute for Health and Care Excellence (NICE)), over the 15-month period from baseline when patients are randomised to PBT or control, until 12 months after surgery.

Secondary analyses will include wider societal costs (e.g. out-of-pocket costs to participants, and productivity losses for patients and informal carers), and will include extending the analysis to the lifetime horizon via a decision analytic model.

Information captured from participants until disease recurrence on the EQ-5D-5L form will be included in this model, along with all other relevant information captured during the trial, supplemented by information from the literature and from the NHS Digital follow-up data wherever possible.

Resource use and costs will be collected from all participants in both arms of the trial covering a period from three months pre-treatment (to control for variation in baseline health care costs across the sample) until 12 months follow-up post-surgery (i.e. around 16 months post-randomisation). Resource use information will be captured via questionnaires at baseline and follow-up timepoints from participants using a modified version of the Client Service Receipt Inventory (CSRI), covering primary and community care, informal/unpaid social care support, out-of-pocket costs and time off work, as well as any secondary care including A&E visits, medications and other therapies that were not given at the trial sites. The trial sites will provide resource use and cost information

on the proton and photon-based therapies, and chemotherapy and immunotherapy and other relevant therapies or diagnostics or other visits provided to participants at these sites. Other case report forms including treatment forms will also be used to provide resource use information. Costs will be calculated by applying national reference costs to the captured resource use information.

Quality of life (QoL) will be collected using the EQ-5D-5L at baseline and key follow-up points (see appendix 1). The EQ-5D-5L will be used to calculate utility values, that will then be used to calculate QALYs over the trial period, using the area under the curve [80] method and adjusting for baseline utility values and other stratification or other important variables in agreement with the statistical analysis.

The mean per-participant differences in costs and QALYs by randomised arm, and the uncertainty around these means (i.e. standard errors and 95% confidence intervals) will be jointly estimated via bootstrapped seemingly unrelated regression to account for the correlation between costs and QALYs, adjusting for baseline values and any minimisation or stratification or other relevant baseline variables in agreement with the statistical analysis. The decision model extending to the lifetime horizon will use probabilistic sensitivity analysis in a similar way to provide mean per-patient lifetime incremental costs and QALYs.

These means and the uncertainty around them will be expressed using cost-effectiveness planes and corresponding cost-effectiveness acceptability curves, to show the probability of the proton therapy pathway being cost-effective vs. control pathway for a range of values of the cost-effectiveness threshold (cost per QALY gained).

Data will be analysed according to randomised groups (i.e. according to intention to treat) and using available-case analysis. The number of missing observations for each outcome at each time point will be reported. Patterns of missingness will be explored, predictors of missingness will be assessed, and the suitability of missing data assumptions considered. Depending on the level and pattern of missing information in each variable, we will consider performing multiple imputation or other types of imputation as appropriate, in consultation with the statistician where appropriate to ensure that the variables that are used in both statistical and health economic analyses are treated in a coherent manner.

A secondary analysis calculating the incremental cost per complication avoided (primary trial endpoint) will also be performed, using the same methods and cost information as described for the primary health economic analysis. Sensitivity and scenario analyses will be undertaken to quantify the uncertainty in the results, including for example using different unit costs for some key therapies including proton beam therapy, based on cost information from sites.

18.4 Interim Analyses

The IDMC will review the efficacy, safety and compliance data at least once a year and will make recommendations to the TSC and TMG.

An IDMC will be scheduled once 40-50 patients have been randomised to the main study to check the toxicity rate. An exact test will be performed to compare the toxicity rate to the hypothesised rate of 45%. If the toxicity rate is significantly higher or lower than the expected rate (45%) in the photon arm, then remaining SCC trial patient slots could be reallocated to adenocarcinoma.

There are no formal rules for stopping for efficacy. There are no formal rules for stopping for futility but at each IDMC meeting, conditional power will be presented. The decision to continue the trial will be influenced by several considerations such as the specific objectives and design of the trial, the disease under study, the treatment approach, the demographic and clinical characteristics of the patient population, alongside other ethical aspects. In this context, a general guideline for informing on whether the trial should continue or not, based on the evaluation of conditional power, is as follows:

- > 80%: Strong likelihood of achieving statistical significance by the end of the trial, suggesting that the current trends are highly likely to continue.
- 50% - 80%: Moderate likelihood of achieving statistical significance, suggesting that the current trends may continue.
- 20% - 50%: Uncertain likelihood of achieving statistical significance, implying that there is a chance that the current trends may not hold.
- < 20%: Minimal likelihood of achieving statistical significance at the end of the trial, indicating that it is unlikely the current trends will result in a positive outcome by the end of the trial.

19 ETHICAL CONSIDERATIONS

This trial will adhere to the principles and conditions of Good Clinical Practice.

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with the protocol and with all relevant guidance, laws and statutes, as amended, applicable to the performance of clinical trials and research including, but not limited to:

- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority
- Human Rights Act 1998
- Data Protection Act 2018
- UK GDPR (as defined in section 3(10) (as supplemented by section 205(4)) of the Data Protection Act 2018); all applicable law about the processing of personal data and privacy; and (to the extent that it applies) the General Data Protection Regulation (EU)2016/679 (EU GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Mental Capacity Act 2005

19.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London - Camden & Kings Cross Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

19.2 Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

19.3 Protocol Amendments

UCL CTC will be responsible for gaining ethical approval, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

19.4 Patient Confidentiality & Data Protection

Patient identifiable data, including name, date of birth, NHS number (or equivalent), postcode, ethnicity, gender and telephone number/email will be collected by UCL CTC via OpenClinica (OC) a remote electronic data capture system used in Clinical Research. UCL CTC will preserve patient confidentiality and will not reproduce or disclose, without prior consent, any information by which patients could be directly identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL.

Twilio and Sinch (also known as Mailgun) are sub-processors of OC. Patient identifiable data will be provided to Twilio (patient name and mobile telephone number) and Sinch (patient name and email address). They will use these details in order to send text messages (Twilio) and/or emails (Sinch) to invite patients to complete online quality of life questionnaires and the Participant Health Care Resource Use Questionnaire (Modified Client Service Receipt Inventory (CSRI). Twilio will process data for sending invitations in the US, where data protection laws have different levels of protection to those in the UK and EU/EEA. Sinch will process data in the EU. Twilio and Sinch are required not to use patient identifiable data for any purposes other than those detailed above. They will not share personal information with any other organisation, they will hold it securely and retain it only for the period required to process the data. UCL CTC will not have access to the patient identifiable data provided for this purpose.

Patient trial number and initials will be provided to the UCL GCLP facility (central laboratory) in order to process the samples. The central laboratory will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

20 SPONSORSHIP AND INDEMNITY

20.1 Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office 4th Floor, West 250 Euston Road London NW1 2PG
Contact:	Managing Director, UCLH/UCL Research
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

20.2 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if it is proven that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

21 FUNDING

Cancer Research UK is supporting the central coordination of the trial through UCL CTC. The Taylor Family Foundation is supporting the exploratory research for PROTIEUS via CRUK.

Proton Beam Treatment is paid for by NHS England directly to the two proton beam centers (The Christie and UCLH).

Research A will be reimbursed to sites as per the finance section of the site agreement.

22 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG. The first publication of the trial results will be in the name of the TMG, if this does not conflict with the journal's policy. The TMG will form the basis of the writing committee and advise on the nature of publications. If there are named authors, these should include the Chief Investigator, Trial Manager(s), and Statistician(s) and Health Economist(s) involved in the trial. Contributing Site Investigators in this trial will also be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by UCL. The ISRCTN number allocated to this trial will be quoted in any publications resulting from this trial.

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APPENDIX 1: QUICK REFERENCE GUIDE TO PATIENT VISITS

Timepoint	Pre-randomisation	Pre-Neoadjuvant SACT	During Neoadjuvant SACT	Pre-CRT Visit	During concurrent Chemoradiation (CRT)[F]	Completion of CRT	**Surgery[M]**	**Adjuvant SACT** (2-weekly) (within 4- 12 weeks post-surgery)	Post Surgery Follow-Up Month 1	Post Surgery Follow Up Month 3 **(PRIMARY ENDPOINT)**	Post Surgery Follow Up Months 6, 9 &12	Completion of adjuvant SACT (including after 1 yr administration, unacceptable AE, IO withdrawal)	Disease Recurrence
	Within 7d pre-randomisation (*unless indicated)	Within 7d prior to starting neoadjuvant SACT	FLOT+/-IO: 2-weekly before cycles 2,3,4. Carbo-taxol: weekly		Chemo: 3 weekly cycles, RT/PBT over 3 consecutive weeks	4-6 weeks post last fraction			4 weeks post surgery +/- 14days	13 weeks post surgery +/- 7days	6, 9 & 12 months post surgery +/- 14days	28-35d post last SACT administration	
Informed Consent*	x												
Histology confirmation of OEC[K*]	x						x						
Upper GI MDT Confirmation of eligibility	X*												
DPYD test	X*												
Whole body PET-CT	x[P]					x[G]					x [R] (6&12m only)		
CT (TAP)[A]	x[P]					x				x	x [R] (6&12m only)	x	x[N]
EUS and Laparoscopy[T]	x												
Medical History	x												
Assessment of AEs	x		x	x	x	x		x	x	x	x	x	x
Physical examination[C]	x		x	x	x	x		x	x	x			
Weight [B]	x[B]		x	x	x			x					
Vital signs[D]	x								x	x			
Mellow dysphagia score	x		x	x	x	x							

Timepoint	Pre-randomisation	Pre-Neoadjuvant SACT	During Neoadjuvant SACT	Pre-CRT Visit	During concurrent Chemoradiation (CRT)[F]	Completion of CRT	**Surgery[M]**	**Adjuvant SACT** (2-weekly) (within 4- 12 weeks post-surgery)	Post Surgery Follow-Up Month 1	Post Surgery Follow Up Month 3 **(PRIMARY ENDPOINT)**	Post Surgery Follow Up Months 6, 9 &12	Completion of adjuvant SACT (including after 1 yr administration, unacceptable AE, IO withdrawal)	Disease Recurrence
	Within 7d pre-randomisation (*unless indicated)	Within 7d prior to starting neoadjuvant SACT	FLOT+/-IO: 2-weekly before cycles 2,3,4. Carbo-taxol: weekly		Chemo: 3 weekly cycles, RT/PBT over 3 consecutive weeks	4-6 weeks post last fraction			4 weeks post surgery +/- 14days	13 weeks post surgery +/- 7days	6, 9 & 12 months post surgery +/- 14days	28-35d post last SACT administration	
ECOG PS	x		x	x	x	x		x	x	x	x (6m only)		
Cardiac function testing[Q]	x[Q]					x			x	x	x		
Pulmonary function test [Q]	x[Q]					x[E,L]			x[E,L]	x[E,L]	x[E,L]		
FBC + differential[U]	x		x	x	x	x		x	x	x	x	x	
Serum biochemistry, renal and liver function[V]	x				x								
Pregnancy test	x	x[H]		x[H]									
QoL (EORTC QLQ-C30 + QLQ-OES18)		x							x	x	x		x
QoL (EQ-5D-5L)		x		x		x			x	x	x		
Participant Health Care Resource Use Questionnaire (Modified CSRI)		x				x			x	x	x		
Post-operative complications									x	x			

Timepoint	Pre-randomisation	Pre-Neoadjuvant SACT	During Neoadjuvant SACT	Pre-CRT Visit	During concurrent Chemoradiation (CRT)[F]	Completion of CRT	**Surgery[M]**	**Adjuvant SACT** (2-weekly) (within 4- 12 weeks post-surgery)	Post Surgery Follow-Up Month 1	Post Surgery Follow Up Month 3 **(PRIMARY ENDPOINT)**	Post Surgery Follow Up Months 6, 9 &12	Completion of adjuvant SACT (including after 1 yr administration, unacceptable AE, IO withdrawal)	Disease Recurrence
	Within 7d pre-randomisation (*unless indicated)	Within 7d prior to starting neoadjuvant SACT	FLOT+/-IO: 2-weekly before cycles 2,3,4. Carbo-taxol: weekly		Chemo: 3 weekly cycles, RT/PBT over 3 consecutive weeks	4-6 weeks post last fraction			4 weeks post surgery +/- 14days	13 weeks post surgery +/- 7days	6, 9 & 12 months post surgery +/- 14days	28-35d post last SACT administration	
(Clavien-Dindo Appendix 4)													
Research blood (cfDNA)		x and germline[J]		x		x			x	x	x	x	x
Surgical photographs for Surgical QA							x						
Confirmation of commencement of immunotherapy treatment									x				
Review of further/additional treatment													x

[A] Contrast enhanced. Neck optional
[B] Weight should be recorded at every visit where indicated, with addition of height to be recorded at screening only
[C] Full physical examination to be completed at screening and C1 neoadjuvant chemotherapy treatment, and all visits thereafter should be targeted physical assessment only
[D] Vital signs should include blood pressure, temperature, heart rate
[E] Not required if CPEX/CPET done (not mandatory but strongly recommended)
[F] Weekly assessment should be done within 72 hours of the start of each chemotherapy cycle
[G] Required only if clinically indicated
[H] Pregnancy test does not need to be repeated if screening test was performed within 7 days of starting CRT.

[J] Must be carried out after randomisation and prior to any chemotherapy delivery
[K] Diagnostic and surgical FFPE samples to be sent to central lab for exploratory research
[L] Pulmonary function test (e.g. cardiopulmonary exercise testing such as CPEX/CPET or lung function tests) (not mandatory but strongly recommended)
[M] Patients that do not have surgery will be followed up as per local policy. Disease recurrence and death should be reported. EQ-5D-5L to be completed.
[N] Other imaging as per local policy

[P] Whole Body PET-CT and CT are both required prior to randomisation, however, only 1 of these scans must be performed within 4-6 weeks prior to randomisation.

[Q] Cardiopulmonary function testing must be performed within 12 weeks pre-randomisation (e.g. ECG and MUGA or ECHO) according to local policy. If it is not possible to complete test pre-randomisation, test must be performed before treatment starts. At completion of CRT treatment and follow-up only ECG is required.
[R] CT and/or PET-CT required at 6 and 12 month follow-up visits

[T] EUS is strongly recommended within 6 weeks prior to randomisation, (but not mandatory) and laparoscopy is strongly recommended within 6 weeks prior to randomisation. Laparoscopy should be performed as per institutional standard of care for GOJ tumours.

[U] Full blood count and differential: Haemoglobin, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count.

[V] Serum biochemistry, renal and liver function: albumin, lactate dehydrogenase (LDH), urea, creatinine, sodium, potassium, bilirubin, aspartate transaminase (AST) and/or alanine transaminase (ALT)

SACT= systemic anticancer therapy

* Tests required before randomisation but no specific time constraint.

APPENDIX 2: EXPECTED ADVERSE EVENTS

A) Radiotherapy

The following AEs are commonly associated with radiotherapy [5, 8] and will be considered expected for photon or proton beam treatment, even if fatal:

System Organ Class	Event term
Blood and lymphatic system disorders	Febrile Neutropenia
Cardiac Disorders	Acute coronary syndrome Cardiac Toxicity Cardiac Conduction disorder/AF Heart failure Pericarditis/ pericardial effusion
Ear and labyrinth disorders	Tinnitus (chemotherapy related)
Gastrointestinal disorders	Diarrhoea Dysphagia Gastrointestinal Fistula/perforation Gastritis/ Gastric ulceration Mucositis Nausea Odynophagia Oesophageal reflux Oesophagitis/oesophageal ulceration Oesophageal perforation (with/without mediastinitis) Oesophageal stenosis Pain (oesophageal) Poor oral intake Tracheo-oesophageal fistula Upper Gastrointestinal Haemorrhage Vomiting
General disorders and administration site conditions	Fatigue Fever
Immune System Disorders	Hypothyroidism
Infections and infestations	Pneumonia
Injury, poisoning and procedural complications	Radiation dermatitis
Investigations	Low Albumin Anaemia Aspartate aminotransferase increased Lymphocyte count decreased Neutrophil count decreased Platelet count decreased Weight loss/failure to thrive/ poor nutritional status
Metabolism and nutrition disorders	Anorexia
Nervous System Disorders	Lethargy

System Organ Class	Event term
Skin and subcutaneous tissue disorders	Skin hyperpigmentation Skin hypopigmentation
Renal and urinary disorders	Chronic Kidney disease
Respiratory, thoracic and mediastinal disorders	Aspiration Pleural effusion Pneumonitis Pulmonary fibrosis

B) Surgery

The table below lists the expected events in relation to surgery and this should be used as the RSI when assessing the expectedness of SAEs causally related to surgery:

Bleeding	**Genitourinary**	**Neurological**
• Anaemia requiring transfusion • Post-operative bleed other than gastrointestinal • Wound haematoma	• Renal failure • Urinary retention	• Delirium / agitation • Loss of consciousness • Vertigo
Cardiac	**Infectious**	**Pulmonary**
• Angina • Arrhythmia • Congestive heart failure • Hypertension • Hypotension • Myocardial Infarction	• Abscess • Fever of Unknown Origin (FUO) • Systemic Sepsis • Urinary Tract Infection (UTI)	• Atelactasis • Pleural effusion • Pneumonia • Pneumothorax • Respiratory distress
Gastrointestinal	**Wound Infection**	**Surgical**
• *Clostridium difficile* colitis • Constipation (inability to have a bowel movement postoperative day 5 with no signs of ileus or SBO) • Diarrhoea • Emesis	• Deep or superficial wound dehiscence • Wound Infection • Wound seroma	• Bowel Injury • Incisional hernia • Retained foreign body • Vascular injury • Thoracic duct injury • Cranial nerve and/or sympathetic chain injury • Brachial plexus injury
Miscellaneous	**Thromboembolic**	
• Acidosis • Decubitis ulcer	• Deep vein thrombosis (DVT)	

• Dehydration • Lymphocele • Peripheral arterial ischemia • Psychological illness • Platelet count decreased	• Superficial phlebitis • Pulmonary embolism	

Note: Many of the side effects to surgery can be exacerbated by CRT (i.e. for all surgical complications we consider them possibly related to CRT)

APPENDIX 3: EASTERN COOPERATIVE ONCOLOGY GROUP SCALE

ECOG Grade	ECOG Status
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

APPENDIX 4: THE CLAVIEN-DINDO CLASSIFICATION [52]

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
IVa	Single organ dysfunction (including dialysis)
IVb	Multi-organ dysfunction
V	Death of a patient

**brain haemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.*

APPENDIX 5: MELLOW SCORING SYSTEM FOR DYSPHAGIA

Grade	Type
0	No dysphagia
I	Dysphagia to solids
II	Dysphagia to soft solids
III	Dysphagia to liquids
IV	Cannot even swallow saliva

APPENDIX 6: TOTAL TOXICITY BURDEN *[81]*

A) Observed Repeatedly

Toxicity	Severity	Severity Weights
Atrial Fibrillation:	Present	30
Pericardial Effusion:	Non-symptomatic	10
	Medical Intervention	60
	Surgical Intervention	90
Pleural Effusion:	Non-symptomatic	10
	Medical Intervention	30
	Surgical Intervention	60
Myocardial Infarction:	Occurrence	70
Pneumonia:	Occurrence	40
Pneumonitis:	Grade 1-2	20
	Grade 3	60
	Grade 4	90

B) Postoperative Complications (Evaluated Once)

Toxicity	Severity	Severity Weights
Anastomotic leak:	Radiographic-only	30
	Medical Intervention	60
	Surgical Intervention	90
ARDS:	Occurrence	90
Pulmonary Embolism:	Occurrence	60
Reintubation:	Occurrence	70
Stroke:	Occurrence	90
Pneumonia:	Occurrence	40
Atrial Fibrillation:	Occurrence	30

APPENDIX 7: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
1.0	26/10/2023	unapproved	-	N/A
1.1	13/12/2023	-	12.4	Clarified that the pregnancy follow-up period is during pregnancy and for up to 6 weeks after.
			15.5	Patients who lose capacity during the trial will be withdrawn from the trial.
2.0	27/06/2024	4	Front page	Added ISRCTN reference number Updated Cancer Research UK logo
			TMG	Change to TMG membership; Alan Sahin replaced Ka Man Mak as SPM. New members added: William Bleaney, Was Mansoor, Sumeet Hindocha
			7.2	Corrected the personal data collected for patients on the observational sub-study (name, telephone number and email are not required, but initials will be collected). Updated the process for registering patients on the observational sub-study.
			8.4.2	International peer review of PBT plans will not be required. Clarified the patients that will have prospective RTQA review as all patients will have a 4DCT.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
			9.1.1	Cardiopulmonary function tests can now be performed within 4-6 weeks prior to randomisation (previously required within 7 days of randomisation). If it is not possible to complete test pre-randomisation, test must be performed before treatment starts. Thyroid function tests are no longer required. PET-CT or CT required prior to randomisation (not both). Laparoscopy + Endoscopy strongly recommended 6 weeks prior to randomisation.
			9.1.5	Clarified that surgery is standard of care and where to find details of surgical QA.
			9.2	Updated the name of the eCRF that needs to be completed for the Observational Sub-study.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
			10.1	Updated terminology from ctDNA (circulating-tumour DNA) to cfDNA (cell-free DNA). Clarification about FFPE tissue blocks required from diagnostic biopsy and surgery. Change to the timing of shipping tissue samples to the central laboratory; previously sent within 3 months of randomisation, and changed to after all patients have completed surgery/upon request of CTC.
			10.2	Clarified that imaging reports and pathology reports are also being collected.
			12.2	SAE processing changes at the CTC: SAEs will not be sent to CI to evaluate causality on behalf of the sponsor.
			14	Clarified that there is no routine on-site or remote monitoring.
			Appendix 1	Updated in line with changes made to section 9.
				Minor corrections and formatting throughout.
3.0	03/04/2025	6	TMG	Changes to TMG membership: Sumeet Hindocha and Jonathan Helbrow are no longer members.
			1.1	ISRCTN reference added

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
3.0	03/04/2025	6	1.2	Trial Schema updated
			2	Background information added for the Checkmate-577 and ESOPEC trials
			6.3.4	Contraceptive advice section updated to account for FLOT chemotherapy.
			7.1	FLOT suitability added as a stratification factor at randomisation
			8.1 and 8.2	Updates to treatment sections due to incorporation of FLOT chemotherapy as neoadjuvant and adjuvant treatments.
			8.4.2	Clarified that there will be prospective individual case review of the radiotherapy plans for at least the first 3 patients in the proton arm *treated* at each PBT centre with UK peer review.
			9.1	Updates to assessments due to incorporation of FLOT chemotherapy as neoadjuvant and adjuvant treatments.
			9.1.1	Introduction of DPYD testing to assess suitability for FLOT chemotherapy
			9.1.1	Correction: PET-CT and CT are both required prior to randomisation, however, only 1 of the scans must be within 6 weeks of randomisation.
			9.1.1	Laparoscopy has been changed from 'mandatory for GOJ tumours', to 'as per institutional SOC for GOJ tumours'.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
3.0	03/04/2025	6	9.1.1	Cardiopulmonary function tests can now be performed up to 12 weeks prior to randomisation (previously 4-6 weeks)
			10	Reminder added that research blood samples must NOT be collected before randomisation.
			10.1	Adjusted time-point for research blood sample to be collected pre-chemoradiation (within 7 days prior to chemoradiation commencing), previously in cycle 1 of neoadjuvant chemotherapy.
			18.2.2	Update to secondary endpoint to incorporate adjuvant chemotherapy: *Time from surgery to commencement of adjuvant immunotherapy or adjuvant chemotherapy*
			18.4	Addition of an IDMC meeting after 40-50 patients to review toxicity data
			Appendix 1	Updates to assessments due to incorporation of FLOT chemotherapy as neoadjuvant and adjuvant treatments and other updates in line with changes to section 9.
				Minor corrections and formatting throughout.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
4.0	01/10/2025	10	TMG	Updated TMG Membership: Added Jillian Blackshaw and Helen Gordon Smith. Removed Sue Campbell (RIP). SPM is now Ka Man Mak.
			6.2	Updated eligibility criteria: Tumours can now be a maximum of 10cm in length in the thorax or up to 12cm in the GOJ or lower 1/3 of the oesophagus, and the total length of disease (tumour + nodes) can be a maximum of 14cm.
			8.2.5	Added a figure showing suggested scheduling for adjuvant FLOT after surgery.
			10	Clarified the full blood count and differential, and serum biochemistry, renal and liver assessments.
			10	Clarified that research samples are just for patients with adenocarcinoma.
			Appendix 1	Clarified the full blood count and differential, and serum biochemistry, renal and liver assessments.
			Appendix 2	Corrected surgical AE from pleural infusion to pleural effusion.
			Appendix 2	Removed list of expected AEs for chemotherapy and immunotherapy as SAEs related to these treatments are exempt from SAE reporting.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
5.0	08/01/2026	11	Title	Trial title updated as standard adjuvant treatment should be given as per local policy
			TMG	Updated TMG Membership: Removed Was Mansoor and William Bleaney
			Trial Schema	Separate schemas to clarify treatment options for OAC and OSCC patients. Treatment options updated to SACT: -Neoadjuvant immunotherapy included as per local policy, and -adjuvant treatment options updated to include FLOT +/- IO for adenocarcinoma patients. Adjuvant SACT treatment as per local policy and not dependent on whether patients have pCR or residual disease.
			Trial Summary	Treatment options clarified and terminology updated to include options of SACT as per local policy: -Neoadjuvant immunotherapy included as an option to add to FLOT chemotherapy as per local policy, and - adjuvant treatment options updated to SACT according to local policy.
			6.3.4	Contraceptive advice updated to include advice for patients receiving durvalumab.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
5.0	08/01/2026	11	8.1 8.2.4 8.2.5	Treatment summary updated to describe options of SACT: -Neoadjuvant immunotherapy as an option to add to FLOT chemotherapy as per local policy, and - adjuvant treatment options updated to add FLOT +/- IO for adenocarcinoma patients as per local policy.
			9	Assessments clarified prior starting neoadjuvant SACT, during adjuvant SACT, prior to CRT, and while on concurrent CRT.
			18.2.2	Secondary endpoints updated due to the addition of SACT
				Minor corrections, clarifications and formatting throughout.

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