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APHRODITE

A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer

Sponsor: University of Leeds

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Trial Summary

Title	A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer
Acronym	APHRODITE
Background	Colorectal cancer is the third most common cancer. Bowel cancer screening is leading to an increase in the number of patients diagnosed with early rectal cancer. Although the standard of care for rectal cancer is radical surgery, an ageing population and increasing numbers of patients with comorbidities means that improved non-surgical approaches are needed for this patient group to live with and beyond cancer. There is growing evidence that an organ preservation approach for early rectal cancer using pelvic chemoradiation (CRT) is feasible and safe. A small prospective single-centre study from Denmark used radiation dose intensification to the primary tumour, delivered with intensity modulated external beam radiotherapy (IMRT) to 60 Gy in 30 fractions, combined with an endorectal brachytherapy tumour boost to 5 Gy. They observed high rates of clinical complete response (cCR) (78%), acceptable acute toxicity (8% grade 3 diarrhoea) and local tumour regrowth of 25% at two years. However, high quality prospective evidence in this important group of patients is lacking and a randomised clinical trial is required to determine whether, compared to standard CRT, radiotherapy dose escalation using IMRT can produce a clinically meaningful increase in the clinical complete response (cCR) rate, with acceptable toxicity and health related quality of life (HRQoL). APHRODITE addresses this question in patients who are considered unsuitable for radical surgery to remove the rectum.
Population	Patients with early stage non-metastatic, biopsy-confirmed rectal adenocarcinoma deemed by their multi-disciplinary team to be unsuitable for radical total mesorectal excision (TME) surgery due to either an increased risk of surgical complications, or marked anxiety at the prospect of a stoma, or expected difficulties managing a stoma post-operatively.
Design	Randomised phase II, multi-centre open-label study.
Objectives	To assess and compare the clinical complete response rate at 6 months post-start of treatment between the treatment groups.

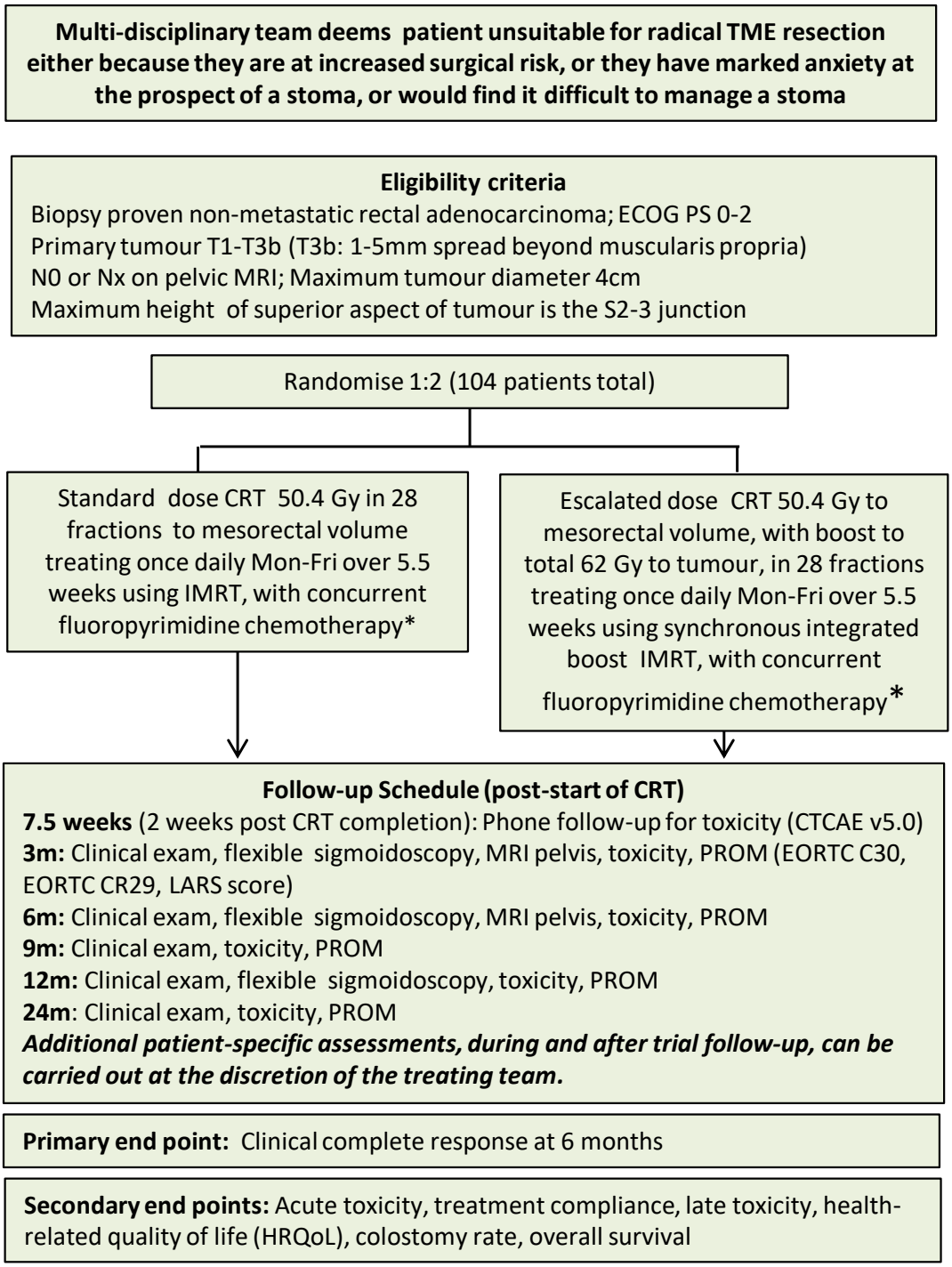
Intervention	**Standard dose CRT (SDCRT) arm**: Radiotherapy using a dose of 50.4 Gy, applied to the primary tumour and surrounding mesorectum using IMRT, in 28 fractions of 1.8 Gy, one fraction per day, 5 days a week. Daily image guidance for treatment delivery. **Escalated dose CRT (EDCRT) arm**: Radiotherapy using a dose of 50.4 Gy applied to surrounding mesorectum and 62 Gy applied to the primary tumour using synchronous integrated boost IMRT, in 28 fractions, one fraction per day, 5 days a week. Daily image guidance for treatment delivery. **The use of concurrent chemotherapy:** There are three options when considering the use of concurrent chemotherapy. Whichever option is chosen for a particular patient will be declared **prior** to randomisation and the declared option will be used whether the patient is randomised to the SDCRT or EDCRT arm. 1. Chemotherapy at 100% dose using Capecitabine 825 mg/m² orally, b.i.d. to be given on radiotherapy days throughout the radiotherapy course. Alternatively, at the discretion of the treating oncologist: Leucovorin (LV) via a short IV push, followed by 5FU 350mg/m^2 in 500ml of normal saline over 1 hour (5FU/LV) is given once per day on radiotherapy days only, during radiotherapy fractions (treatments) 1-5 and 21-25. 2. Chemotherapy at 75% dose of either capecitabine or 5FU/LV, if there are concerns regarding a particular patient's ability to withstand 100% dose. 3. Alternatively, chemotherapy can be omitted entirely if the patient is not thought to be able to tolerate any chemotherapy in the view of the treating team.
Sample size	104 patients
Follow Up	All participants will be followed up, initially via a phone call at 2 weeks following CRT completion (approximately 7.5 weeks from treatment start), then via clinical visits at 3, 6, 9, 12, and 24 months from treatment start.
Primary Endpoint	Clinical complete response rate at 6 months post-start of treatment assessed via a composite of digital examination, high resolution pelvic MRI and sigmoidoscopy.

Secondary Endpoint	Acute toxicity, treatment compliance, late toxicity, patient reported outcome measures (PROMs) including health-related quality of life (HRQoL), stoma rate, overall survival.

Main Inclusion Criteria	• Biopsy confirmed adenocarcinoma of the rectum
	• Age 18 or over
	• Able to provide written informed consent
	• MDT deems patient unsuitable for radical TME surgical resection of their tumour either because they are considered to be at increased surgical risk from TME (for example due to general frailty or due to specific co-morbidities which make anaesthetic or surgery hazardous, such as cardiac disease, pulmonary disease, renal failure, previous anaesthetic problems or previous pelvic surgery), or they have marked anxiety at the prospect of a stoma, or because of anticipated difficulty managing a stoma post-operatively (including physical causes such as arthritis, Dupuytren's contracture and visual problems).
	• Patient is suitable for either pelvic radiotherapy or chemoradiation in the opinion of the treating oncologist
	• ECOG PS 0-2
	• Primary tumour is ≤ 4 cm in maximum diameter
	• Primary tumour is staged at T1-T3b. (TNM staging as per UICC 8th Edition (Appendix B), with additional T3 subdivisions)
	• Tumour is visible on MRI
	• Superior aspect of tumour is at or below a horizontal line drawn from the anterior aspect of the S2/3 junction on pre-treatment MRI
	• No unequivocally involved lymph nodes, i.e. *NX (nodes too small to characterise as to say equivocal nodes) and N0 are both eligible*
	• For low rectal tumours superior to the puborectalis sling, patients are eligible if the mesorectal fascia or levator are:
	  o Clear (>1 mm from disease to levator ani or mesorectal fascia)
	  o or threatened (≤1mm from disease to levator ani or mesorectal fascia)
	  o or mesorectal fascia is involved but not breached
	• For patients intended to receive radiotherapy alone, or concurrent 5-Fluorouracil, there is no required level of renal function. Patients intended to receive capecitabine require an estimated creatinine clearance ≥ 30 ml/min (estimated using a validated creatinine

	clearance calculation e.g. Cockroft and Gault (Appendix D) or Wright formula) • Absolute neutrophil count > 1.5 x 10^9/l; platelets > 100 x 10^9/l • Serum transaminase concentration < 3 x Upper Limit Normal (ULN) • Bilirubin concentration < 1.5 x ULN
Main Exclusion Criteria	• Nodal involvement identified by nodes showing irregular margins and or heterogeneous signal on the high resolution MRI (i.e. N1-N2) • The presence of EMVI discontinuous with the primary tumour • Discontinuous tumour deposits (N1c) • Dominant mucinous tumour on MRI • Signet ring carcinoma or tumours histopathologically containing a neuroendocrine component • Tumour has grown through and breached mesorectal fascia • Tumour involves or breaches the levator ani (as this would be T4b disease) • Involvement of anal intersphincteric plane or external anal sphincter or adjacent organs *(If the participant has a low rectal tumour extending inferior to the puborectalis sling, involvement of the internal anal sphincter is permitted)* • Undergone an attempt at complete local resection of their cancer • Previous pelvic radiotherapy • Definite distant metastases *(equivocal distant metastases on the CT scan are permitted, e.g. indeterminate lung modules, sub-centimetre retroperitoneal nodes or indeterminate liver lesion)* • Defunctioning colostomy or ileostomy has been fashioned • Prior invasive malignancy unless disease free for a minimum of 3 years (excluding basal cell carcinoma of the skin or other in situ carcinomas) • Prior systemic chemotherapy for colorectal cancer • Women who are pregnant, breastfeeding or a women of child bearing potential who are unwilling to use effective contraceptive methods
Randomisation	Two arm randomisation (1:2) to SDCRT versus EDCRT.

APHRODITE Trial Schema



*At treating team discretion, concurrent chemotherapy can be used either at 75% dose or omitted completely. This choice must be declared prior to randomisation.

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2 Abbreviations

Abbreviation	Definition
5FU	5-Fluorouracil
AAPM	American Association of Physicists in Medicine
ADL	Activities of daily living
AE	Adverse event
AR	Adverse reaction
ASA	American Society of Anaesthesiologists
B.I.D	Twice a day
BNF	British National Formulary
cCR	Clinical Complete Response
CI	Chief investigator
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
CT	Computerised tomography
CTV	Nodal Clinical Target Volume
CV	Curriculum vitae
DCE	Discrete choice experiment
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucleic acid
DRE	Digital Rectal Examination
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	The European Organisation for Research and Treatment of Cancer
EDCRT	Escalated dose chemoradiation
FFPE	Formalin fixed paraffin embedded

GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
Gy	Gray (unit of ionising radiation)
GTVp	Primary Gross Tumour Volume
H&E	Haematoxylin & Eosin
HR	Hazard ratio
HRA	Health Research Authority
HRQoL	Health-related quality of life
ICRU	International Commission of Radiation Units
ICMJE	International Committee of Medical Journal Editors
IHC	Immunohistochemistry
IMRT	Intensity modulated radiotherapy
ISF	Investigator site file
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LARS Score	Low Anterior Resection Syndrome Score
LFTs	Liver Function Tests
LV	Leucovorin
MDT	Multidisciplinary team
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
MRI	Magnetic resonance imaging
mrTRG	MRI Tumour Regression Grade
MV	Megavoltage
NBOCA	UK National Bowel Cancer Audit
NBSP	NHS Bowel Screening Program
NCI	National Cancer Institute
NCRI	National Cancer Research Institute

NIHR	National Institute of Health Research
NHS	National Health Service
Non-CTIMP	Not a trial of an investigational medicinal product
OAR	Organ at risk
OS	Overall survival
pCR	Pathological complete response
PH	Proportional hazards
PI	Principal investigator
PIS	Patient information sheet
PPI	Patient and public involvement
PS	Performance Status
PPE	Palmar plantar erythema
PROMs	Patient reported outcome measures
PTV_Opt	PTV outside PTVp
PTV	Nodal Planning Target Volume
PTVp	Primary Tumour Planning Target Volume
QA	Quality assurance
QoL	Quality of life
REC	Research ethics committee
RGF	Research Governance Framework
RNA	Ribonucleic acid
RT QA	Radiotherapy Quality Assurance
RTTQA	Radiotherapy Trials Quality Assurance
RUSAE	Related unexpected serious adverse event
SACT	Systemic anti-cancer treatment
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
S:CORT	Stratification in Colorectal Cancer
SDCRT	Standard dose chemoradiation
SOP	Standard operating procedure
SPC	Summary of Product Characteristics

TME	Total mesorectal excision
TMG	Trial management group
TPN	Total parenteral nutrition
TRG	Tumour regression grade
TSC	Trial Steering Committee
YCR	Yorkshire Cancer Research
UICC	Union for International Cancer Control
U&Es	Urea and Electrolytes
ULN	Upper limit of normal
VMAT	Volumetric arc therapy

3 Background and rationale

3.1 Standard of care/surgical morbidity

Colorectal cancer is the third most common cancer in the UK, with 41,000 newly diagnosed cases per year and one third of these situated in the rectum. For patients who present with localised rectal cancer, radical surgery combined with a selective use of pre-operative radiotherapy and adjuvant chemotherapy is the standard of care. Radical surgery for rectal cancer consists of total mesorectal excision (TME), which is an oncologically effective treatment for early stage rectal cancer; only 2% and 12% of patients will experience local or distant failure respectively (Bentrem 2005, Endreseth 2005, Peeters 2007, Sebag-Montefiore 2009). However, radical surgery is associated with risks of operative mortality, significant morbidity, and the frequent need for a temporary or permanent stoma.

Post-operative mortality: The Dutch TME trial reported six-month mortality following radical curative surgery for rectal cancer of 4.6% for patients aged 65-74 years, rising to 13.4% for patients aged 75-84 years (Kapiteijn 2001, Tekkis 2003). Post-operative mortality is also highly dependent on patients' general physical fitness, with significantly increased 30-day mortality in American Society of Anaesthesiologists (ASA) grade III and above patients (Rutten 2008).

Surgical morbidity: Pelvic dissection may inadvertently cause autonomic nerve damage leading to urinary incontinence or retention (25%-34%) and sexual dysfunction (Hendren 2005, Wallner 2008). More than half of all patients experience some form of faecal incontinence following primary TME surgery and 30-40% suffer daily symptoms of urgency, incomplete emptying and stool frequency (Engel 2003, Temple 2005). Three prospective cohort studies have examined health related quality of life (HRQoL) scores following rectal cancer surgery (Engel 2003, Grumann 2001, Wilson 2008). Each demonstrated persistently poor social role, body image, and defaecation scores. Anastomotic leak following surgery is also a significant problem, occurring in approximately 11% of patients (Sauer 2004).

Postoperative stomas: Resection of a low rectal tumour usually requires a permanent stoma. Many more patients have a temporary stoma – a proportion of which may never be reversed. The UK National Bowel Cancer Audit 2016 (NBOCA 2016) showed that overall, 83% of rectal cancer patients had a stoma following major resection. 77% of anterior resections were covered by a defunctioning stoma, but 18 months later only 66% of these patients had undergone stoma reversal. Many were never reversed. Stoma-related morbidity is a significant problem, affecting at least 50% of patients in the form of a high-output stoma, stoma prolapse, small bowel obstruction and wound infection (Bakx 2004).

3.2 Non-surgical management of rectal cancer - Organ preservation

An alternative approach to radical surgery is the use of chemoradiotherapy (CRT) to try to achieve a sustained clinical complete response (cCR). This approach has been successful in the management of squamous cell carcinoma of the anus. Three phase III trials performed in

three regions of the world demonstrated the clinical effectiveness of CRT as initial treatment in anal cancer, resulting in local control rates of around 60%. These trials changed routine clinical practice. In the UK, the UK ACT1 trial changed the standard of care from radical surgery to CRT (Downing 2015). However, in rectal cancer, this approach is not the standard of care and further research is needed.

When standard dose CRT for rectal cancer is used, it results in a significantly lower cCR rate than for anal cancer. Habra- Gama et al in Brazil has pioneered the approach, reporting that up to 40% of patients have sustained local control without radical surgery (Habr-Gama 2006, Habr-Gama, Habr-Gama 2010, Habr-Gama 2011, Habr-Gama 2014). However, these results are from a single centre without tightly defined selection criteria, and most other small series have been unable to reproduce such high cCR and local control rates. Other investigators have reported on the use of organ preservation as an 'opportunistic' approach in patients with locally advanced rectal cancer, where the risk of pelvic failure is relatively high and pre-operative CRT followed by surgery is the standard of care.

Although not yet standard of care, for patients in whom post-CRT endoscopy and magnetic resonance imaging (MRI) suggest a clinical complete response (cCR), a policy of 'active surveillance' is increasingly being adopted in standard clinical practice, to attempt organ preservation and avoid surgery. Studies suggest that patients achieving a cCR have a limited risk of local regrowth. Renehan et al (Renehan 2016) reported the outcome of 129 patients with cCR, with 34% local regrowth and similar cancer outcomes to a matched cohort of surgically managed patients. The recently-published International Watch and Wait Database international multicentre registry study (Van der Valk 2018) is likely to be influential in further adoption of this strategy into standard practice. In 880 cCR patients, 25% exhibited local regrowth, of which the majority (88%) occurred in the first two years with 97% located in the bowel wall and surgically salvageable. A minority of patients (8%) developed distant metastases. 5-year disease-specific survival was 94% and overall survival 85%. A recently published systematic review of 23 studies reporting on patient cohorts managed non-surgically following cCR after CRT echoed these findings, reporting a pooled 2-year local regrowth rate of 21.3% in 575 cCR patients, the vast majority (93.2%) of which were subsequently managed with salvage surgery (Sammour 2017).

The main disadvantage of an 'opportunistic' approach is that only a small minority of locally advanced rectal cancers achieve a cCR with standard dose CRT. Such data provides no information concerning the potential benefit of treatment intensification, including radiotherapy dose escalation. In addition, no information on the long-term effects on HRQoL are provided. These issues can only be addressed through a prospective randomised study, as in the current APHRODITE protocol.

3.3 Rationale for inclusion of early rectal cancers in APHRODITE

APHRODITE focuses on patients with early stage rectal cancer. A relatively higher response rate to standard dose CRT is seen for early rectal cancer: An individual patient meta-analysis of 2,323 patients treated with CRT and subsequently resected demonstrated a correlation between the clinical T-stage and the pathological complete response (pCR) rate (cT1 58%, cT2 28%, cT3 16%, cT4 12%) (Maas 2010). The case mix of newly diagnosed rectal cancer is changing due to the impact of the NHS Bowel Screening Program (NBSP) that was introduced in 2006. The proportion of UICC stage 1 rectal cancer has increased from 13% in 2006 to 23% in the UK (Eva Morris, 2018 – personal communication).

The early stage cancers included in APHRODITE have primary tumour confined to the bowel wall (T1, 2) or with no more than 5mm of extramural spread (T3a-b), with no MRI evidence of extramural venous invasion (EMVI-) and no definite lymph node involvement (N0 or Nx) – a definition aligned with other early stage rectal cancer trials in the UK (STAR-TREC, OPERA). For these patients, the cCR rate following CRT, based on published studies and taking case mix into account, is likely be around 35% (Maas 2010, Garcia-Aguilar 2012, Appelt and Jakobsen 2015). There is therefore a need to determine whether the cCR rate can be improved in this patient group.

3.4 Concurrent Capecitabine chemotherapy

Capecitabine is an oral prodrug of 5-fluorouracil. It is widely used in the UK for the treatment of patients with colorectal cancer both in the adjuvant and palliative settings as a monotherapy, and in combination, with oxaliplatin and irinotecan. It is also used in rectal cancer neo-adjuvant treatment, in combination with radiotherapy. Within the NSABP R-04 trial it was compared with 5-Fluorouracil (5FU) during CRT and shown to be equivalent in terms of locoregional control (Allegra 2015), similarly in a German study (Hofheinz 2012).

The use of a concurrent fluoropyrimidine with radiotherapy is a UK standard of care in rectal cancer pre-operative CRT, often using either oral capecitabine or intravenous (IV) 5FU and leucovorin (5FU/LV). The main side effects using these drugs are diarrhoea, fatigue, nausea, leukopenia and radiation dermatitis (Hofheinz 2012). Patients who are generally frailer with a reduced performance status, or who have specific co-morbidities, may have a reduced tolerance of such side effects. A less common side effect, relevant to an older age group who may have cardiac morbidity, is coronary vasospasm. In UK standard clinical practice it is commonplace for such patients to either receive an elective dose reduction of their chemotherapy (e.g. to 75%), or to omit chemotherapy completely and treat with radiotherapy alone. It is known that in early rectal cancer, radiotherapy alone is also an effective approach (Bujko 2013).

3.5 Rationale for evaluating radiotherapy dose escalation in early stage rectal cancer

Standard CRT in the preoperative setting uses 45-50.4 Gy combined with a fluropyrimidine (Glimelius 2013). Appelt et al published a modelling study based on data from two prospective trials with several different dose levels. This study indicated the existence of a dose-response relationship between tumour radiation dose and pathological response rate (Appelt 2013).

A prospective single-centre study from Denmark, published in 2015 (Appelt 2015), used radiation dose intensification to the primary tumour delivered with intensity modulated radiotherapy (IMRT) to 60 Gy in 30 fractions over 6 weeks with 50 Gy to the pelvic nodes, combined with an endorectal brachytherapy tumour boost to 5 Gy and tegafur/uracil on treatment days. Of 51 treated patients with early stage (T2-3) distal rectal cancer, 40 (78%) had a cCR and were allocated to observation. Grade 3 diarrhoea was observed in four (8%) patients. Local recurrence was 16% and 26% at one and two years respectively for those achieving a cCR. Rectal bleeding was relatively frequent in this study during follow-up, with the high mucosal dose resulting from the brachytherapy boost likely to be a significant factor. Although long-term function was considered acceptable, some rectal dysfunction and faecal incontinence were seen at follow-up. This study provides strong support for dose escalation. However, the major limitation of this study is that it was a single arm, single treatment centre design, meaning that the benefit of dose escalation over standard radiotherapy dose cannot be assessed.

The same Danish group are performing a subsequent multi-centre single arm study (NCT02438839), using external beam dose escalation to 62 Gy in 28 fractions to the tumour. This design removes the brachytherapy boost but again suffers from its non-randomised nature.

There is therefore a strong justification to perform a randomised study using standard dose and dose escalated CRT in early stage rectal cancer in the UK. The key research question is 'Does radiotherapy dose escalation increase the cCR rate, with acceptable toxicity?' This question can only be addressed by a randomised clinical trial that compares standard versus escalated dose radiotherapy.

3.6 Proposed APHRODITE study group

In patients who are not suitable for radical surgery, radiotherapy is commonly used to try to achieve local control and avoid palliative surgery or stoma formation. Early survival may be improved in elderly patients with rectal cancer demonstrating a cCR after radiotherapy if radical surgery is avoided (Smith 2015). Our proposed study will address the benefits of standard dose versus escalated dose CRT in a group of patients with early rectal cancer who are not considered suitable for radical TME surgery in the opinion of their MDT, either because they are at increased risk of surgical complications, or have marked anxiety at the prospect of a stoma, or would have difficulty managing a stoma following surgery.

There is currently a UK National Institute of Health Research (NIHR) portfolio gap, where this group of patients is not eligible to enter the current STAR-TREC or OPERA trials, which both mandate radical surgical resection as standard (STAR-TREC) or at failure to achieve a cCR with CRT (OPERA).

3.7 The use of advanced radiation techniques

Modern radiotherapy techniques, including IMRT and volumetric arc therapy (VMAT), allow increased conformality of treated volumes, reducing the radiotherapy dose delivered to the surrounding organs at risk. This opens the possibility of delivery of increased dose to the tumour with external beam irradiation, without excessive morbidity to surrounding normal tissues, thereby potentially reducing short and long-term toxicity compared to conventional 3D conformal planning (Appelt 2016). IMRT provides the technical solution to dose intensify the gross tumour volume at the primary site without prolonging overall treatment time. The planned dose escalation can be achieved without significantly altering the dose and volume delivered to the organs at risk.

A radiotherapy approach for early stage rectal cancer that treats a mesorectal target volume only has been developed for the STAR-TREC trial (Appelt 2017). This target volume is smaller than used in routine UK clinical practice for locally advanced rectal cancer, as initially developed for the ARISTOTLE trial (CI Sebag-Montefiore), but is appropriate for early stage rectal cancer, where microscopic disease is highly likely to be confined to the mesorectum. This mesorectal only volume is being used in the current STAR-TREC trial. This negates the need to treat larger pelvic lymph node volumes relevant in more advanced disease and is hoped to reduce treatment toxicity.

Based on experience from anal cancer (where internationally doses of 60 Gy or more are used in several countries), and supported by preliminary data from an ongoing Danish study (see above), 62 Gy appears safe when delivered to a confined target volume. In order to allow for normal tissue recovery, this high dose has to be delivered over 28 treatment fractions. Precise daily treatment delivery is achieved by the use of daily image guidance (a cone beam CT scan performed on the treatment machine on each day of treatment). This daily image guidance is essential for these small, carefully defined treatment targets, as both the mesorectum and the tumour itself exhibit significant changes in day-to-day position (Nijkamp 2009, Maggiulli 2012).

3.8 Defining clinical complete response (cCR) following chemoradiation

The goal of an organ preservation strategy is to achieve a cCR and then follow the patient to ensure that this is sustained. cCR can be assessed by clinical examination, endoscopy (sigmoidoscopy) and imaging using pelvic MRI. Maas et al adopted a particularly rigorous definition of cCR, including MRI, endoscopy and biopsies (Maas 2011). Combining MRI and

endoscopy to assess cCR increases sensitivity (Maas 2015), and increasing consensus favours a 'two-step' approach, assessing at 3 then 6 months after CRT start, to allow full maturation of cCR; 90% of patients with a 'near' cCR at 3 months will evolve into full cCR at 6 months (Hupkens 2018). This group and others have moved away from the use of biopsies. In anal cancer, it has recently been reported that when clinical and imaging assessment was performed, the optimal time to determine cCR is at 6 months (Glynne-Jones 2017).

In our proposed study, we focus on cCR at 6 months after the start of CRT as the primary endpoint. This is seen as the best objective measure in a group of patients who are unsuitable for surgery, aiming to achieve local disease control and avoid the morbidity of uncontrolled local disease, together with the need for a defunctioning stoma. The primary endpoint chosen for APHRODITE is strictly defined, not allowing superficial ulceration (Maas 2015) (Section 12.1). Additionally, patients are followed further to 24 months, with important secondary end points including HRQoL.

3.9 Understanding the patient perspective and experience

Studies of non-surgical management and organ preservation for rectal cancer patients have focused on clinical endpoints, e.g. cCR rate, permanent stoma rate, local control, and overall survival, as well as the clinicians' interpretation of patient outcome. There is very little data on patient-reported outcomes (PROMs) following nonsurgical management. The study by Appelt et al (Appelt et al 2015) provides the best data, but this is limited to less than 40 patients treated within a single centre, single arm study. It is therefore important to collect such data prospectively; the current proposal will measure PROMs for the two different radiotherapy doses up to 24 months post- start of treatment, providing a unique dataset.

There is also an almost complete lack of understanding of how patients weight and prioritise different potential outcomes, including the balance between efficacy and toxicity, in the setting of non-surgical rectal cancer treatment. The decision regarding which severity of treatment related toxicities is acceptable for a given organ preservation strategy has previously been evaluated purely by clinicians, despite the obvious need to approach this from the patients' perspective. Previous studies in colorectal cancer surgical studies indicate that patients differ in how they value and weight different outcomes compared with clinicians (Solomon 2003, Harrison 2008, Masya 2009, Currie 2014).

A single study in rectal cancer has examined patient preferences for organ preserving and surgical treatment approaches (Cowenberg 2018) and found similar high variation. No studies so far have focused specifically on patient attitudes to outcomes following non-surgical management of rectal cancer. The current trial has been developed with patient and public involvement (PPI) representatives from the earliest stage. Additionally, a separate patient perspective study using discrete choice methodology (Clark 2014) has been planned to run alongside the APHRODITE trial (Chief Investigator, Dr Edward Webb). This will in practice consist of a short questionnaire to be offered to patients who are candidates for radical

radiotherapy; including patients who go on to participate in APHRODITE, patients who ultimately decline APHRODITE participation, and patients who do not fulfil all trial inclusion criteria (Appendix F, Section 25). The study will have a study protocol and ethics approval separate from the currently trial, and is consequently not covered in detail here.

3.10 Translational Research

It is of interest to assess whether baseline biological radiosensitivity signatures, such as those derived from RNA expression, can predict patients who may benefit more from radiotherapy dose escalation. Conversely can biomarkers of radioresistance predict those who will not? Pre-treatment routine diagnostic formalin fixed paraffin embedded (FFPE) tumour biopsy tissue samples will be collected on all patients and sent to Leeds Institute of Cancer and Pathology, University of Leeds, for storage. The glass Haematoxylin & Eosin (H&E) stained slides will be scanned to create a digital pathology resource for quality assurance (QA) of the trial and support translational research on the tissue. The tissue will later be used for immunophenotyping, DNA analysis and RNA exome analysis.

The UK Stratification in Colorectal Cancer (S:CORT) consortium has established pipelines for handling rectal cancer biopsies through the University of Leeds pathology laboratory, enabling efficient RNA extraction and analysis, DNA extraction and sequencing and digital pathology assessment of H&E slides, together with Immunohistochemistry (IHC) on further sections from the biopsy. Preliminary data from the S:CORT consortium will be further explored in data from APHRODITE. Patients will therefore be asked for consent to use their pre-treatment biopsies for future research.

4 Aims and Objectives

4.1 Aim

To assess whether radiotherapy dose escalated CRT increases the cCR rate, compared with standard dose CRT, with acceptable toxicity, in patients with early stage rectal cancer who are considered unsuitable for radical TME surgery in the opinion of the treating MDT.

4.2 Primary objective

To assess and compare the cCR rates at 6 months post start of treatment between the treatment groups.

4.3 Secondary objectives

To assess and compare between the treatment groups:

- Acute toxicity
- Treatment compliance
- Late toxicity
- PROMs including HRQoL
- Stoma rate
- Overall survival

See Section 12 for full definitions of the primary and secondary endpoints.

5 Trial design overview

APHRODITE is a phase II, multi-centre, open-label, randomised-controlled trial of IMRT, with select use of concomitant chemotherapy, in patients with early stage rectal cancer who are deemed by their Multidisciplinary team (MDT) not suitable for radical TME surgery because either: 1. The patient is thought to be at increased surgical risk due to specific medical co-morbidity or general frailty or 2. The patient has marked anxiety at the prospect of having a stoma or 3. It is anticipated that the patient would have difficulty managing a stoma post-operatively e.g. due to physical problems. The primary aim is to assess whether radiotherapy dose escalation increases the cCR rate at 6 months from the start of CRT, compared with standard radiotherapy dose CRT, with acceptable toxicity. A composite definition for cCR is used including rectal digital examination, rectal endoscopy and pelvic MRI. A total of 104 eligible patients will be recruited from 10-12 UK radiotherapy sites and their associated cancer units and randomised on a 1:2 basis to receive either standard dose chemoradiation (SDCRT) or escalated dose chemoradiation (EDCRT).

Concurrent chemotherapy will be used during CRT, either as single agent oral capecitabine given twice per day Monday-Friday on the days of radiotherapy throughout the course of radiotherapy, or alternatively as IV 5FU/LV delivered once per day concurrent with fractions 1-5 and 20-25 of radiotherapy (weeks 1 and 5).

If the treating team feel that the patient is not fit enough to receive the full (100%) dose of concurrent capecitabine or 5FU/LV, because of specific co-morbidities, or general frailty, then there are the options either to treat with concurrent capecitabine or 5FU/LV chemotherapy at 75% dose, or to omit the chemotherapy altogether and treat with radiotherapy alone. The intended chemotherapy treatment option must be declared for each individual patient PRIOR to randomisation.

Patients will be followed up until 24 months from the commencement of CRT. Patients on trial should not receive any further local or systemic treatment until assessment of the primary endpoint at 6 months. Following identification of residual disease at the 6-month primary endpoint, or local or distant disease progression at any time, management is as according to the local MDT decision. Under these circumstances the treating team are encouraged to review the original decision as to whether the patient remains unsuitable for salvage surgery or not, and to offer surgery if deemed appropriate.

The treating team are encouraged to decide on an individual patient basis whether additional disease surveillance assessments are needed in the follow-up period, over and above those mandated in the APHRODITE protocol (Section 10.5). It has been confirmed with the UK Medicines and Healthcare products Regulation Agency (MHRA) that APHRODITE is not a trial of an investigational medicinal product (non-CTIMP).

6 Eligibility

Patients meeting all of the inclusion criteria and none of the exclusion criteria will be considered for participation in the trial. Eligibility waivers to any of the inclusion and exclusion criteria are not permitted.

6.1 Inclusion criteria

- Biopsy confirmed adenocarcinoma of the rectum
- Age 18 or over
- Able to provide written informed consent
- MDT deems patient unsuitable for radical TME surgical resection of their tumour either because they are considered to be at increased surgical risk from TME (for example due general frailty or due to specific co-morbidities which make anaesthetic or surgery hazardous, such as cardiac disease, pulmonary disease, renal failure, previous anaesthetic problems or previous pelvic surgery), or because the patient has marked anxiety at the prospect of a stoma, or because of anticipated difficulty managing a stoma post-operatively (including physical causes such as arthritis, Dupuytren's contracture and visual problems).
- Patient is suitable for either pelvic radiotherapy or chemoradiation in the opinion of the treating oncologist
- ECOG PS 0-2
- Primary tumour is ≤ 4 cm in maximum diameter
- Primary tumour is staged at T1-T3b. (TNM staging as per UICC 8th Edition (Appendix B), with additional T3 subdivisions)
- Tumour is visible on MRI
- Superior aspect of tumour is at or below a horizontal line drawn from the anterior aspect of the S2/3 junction on pre-treatment MRI
- No unequivocally involved lymph nodes, i.e. NX (nodes too small to characterise as to say equivocal nodes) and N0 are both eligible
- For low rectal tumours superior to the puborectalis sling, patients are eligible if the mesorectal fascia or levator are:
- Clear (>1 mm from disease to levator ani or mesorectal fascia)
- or threatened (≤1mm from disease to levator ani or mesorectal fascia)
- or mesorectal fascia is involved but not breached
- For patients intended to receive radiotherapy alone, or concurrent 5-Fluorouracil, there is no required level of renal function. Patients intended to receive capecitabine require an estimated creatinine clearance ≥ 30 ml/min (estimated using a validated creatinine clearance calculation e.g. Cockroft and Gault (Appendix D) or Wright formula)
- Absolute neutrophil count > 1.5 x 10^9/l; platelets > 100 x 10^9/l

- Serum transaminase concentration < 3 x Upper Limit Normal (ULN)
- Bilirubin concentration < 1.5 x ULN

6.2 Exclusion criteria

- Nodal involvement identified by nodes showing irregular margins and or heterogeneous signal on the high resolution MRI (i.e. N1-N2)
- The presence of EMVI discontinuous with the primary tumour
- Discontinuous tumour deposits (N1c)
- Dominant mucinous tumour on MRI
- Signet ring carcinoma or tumours histopathologically containing a neuroendocrine component
- Tumour has grown through and breached mesorectal fascia
- Tumour involves or breaches the levator ani (as this would be T4b disease)
- Involvement of anal intersphincteric plane or external anal sphincter or adjacent organs *(If the participant has a low rectal tumour extending inferior to the puborectalis sling, involvement of the internal anal sphincter is permitted)*
- Undergone an attempt at complete local resection of their cancer
- Previous pelvic radiotherapy
- Definite distant metastases *(equivocal distant metastases on the CT scan are permitted, e.g. indeterminate lung modules, sub-centimetre retroperitoneal nodes or indeterminate liver lesion)*
- Defunctioning colostomy or ileostomy has been fashioned
- Prior invasive malignancy unless disease free for a minimum of 3 years (excluding basal cell carcinoma of the skin or other in situ carcinomas)
- Prior systemic chemotherapy for colorectal cancer
- Women who are pregnant, breastfeeding or a women of child bearing potential who are unwilling to use effective contraceptive methods

Participants meeting any of the exclusion criteria are not eligible to be enrolled in the trial.

6.3 Birth control

Female patients of childbearing potential should be advised to avoid becoming pregnant while receiving chemoradiotherapy. Male patients who are sexually active with a woman of childbearing potential should be advised to use barrier contraception during chemoradiotherapy and until 6 months after finishing treatment.

6.4 Prior and concurrent participation in other clinical trials

Participation in therapeutic clinical trials is not permitted up to the 6 month primary endpoint assessment. However, participation in non-therapeutic registry studies or questionnaire-based studies is permitted. Questions about potential clinical trials can be addressed to the Chief Investigators via Leeds Clinical Trials Research Unit (CTRU).

7 Participating Sites and Investigators

7.1 Participating sites

Each participating site must be able to comply with the following, as applicable to the trial activities taking place at the site:

- Trial treatments, imaging, clinical care, follow-up schedules and all requirements of the trial protocol.
- Requirements of the Research Governance Framework and amendments.
- Data collection requirements, including adherence to, remote data capture, paper case report forms (CRFs) compliance and electronic case report forms (eCRFs) submission timelines as per Section 10.
- Collection, preparation and shipment of biological samples (pre-treatment biopsies) for future translational research.
- Monitoring requirements as outlined in Section 15.

7.2 Principal Investigators and co-investigators

Sites must have an appropriate Principal Investigator (PI) authorised by the site and ethics committee to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. Investigators involved in the treatment and care of patients must be medical doctors and have experience of treating rectal cancer.

7.3 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 authorised personnel log.

CVs for all staff must be kept up-to-date, signed, dated and copies (or statement of their location) held in the Investigator Site File (ISF) held at site. An up-to-date, signed copy of the CV for the PI must be forwarded to the CTRU prior to site activation.

Good clinical practice (GCP) training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials. Evidence of current GCP training for the PI must be forwarded to the CTRU prior to site activation.

7.4 Radiotherapy quality assurance

The radiotherapy quality assurance (QA) programme will be implemented by the National Cancer Research Institute (NCRI) Radiotherapy Trials Quality Assurance (RTTQA) group to ensure treatment is planned and delivered according to the trial protocol. A summary of the RTTQA requirements are provided in the APHRODITE Radiotherapy Guidelines.

7.5 Site initiation

Before a site is activated, the CTRU trial team will arrange a site initiation. The site initiation will be an electronic process and a site initiation recorded link with the initiation presentations will be sent to the site.

The site initiation link will come with the site initiation training log, which will need to be completed. Best practice would include other related trial specific staff who work on the trial, as a minimum the PI, radiotherapy physicist, research radiographer and research nurse must watch the site initiation video recorded link and slide presentation.

The site initiation recorded link and presentation will act as the site initiation and will cover all areas of the trial and management at site.

The following areas will be covered:

- Trial overview and management.
- Data collection and process
- Safety reporting.
- Essential documentation required for trial

Trial specific staff are required to go through the site initiation link and watch the site initiation presentations, then record on the site initiation training log that they have completed the site initiation training.

A site cannot open to APHRODITE without the site initiation, the site staff assigned to work on the APHRODITE trial must watch the site initiation video recorded presentation, complete the site initiation training log and return this to the APHRODITE team. The signed initiation training log must be returned to aphrodite@leeds.ac.uk. Once all documentation is returned an email confirming that the site initiation has been successful will be issued.

Any questions or queries regarding the trial can also be sent via email to the aphrodite@leeds.ac.uk inbox or a meeting can be arranged to discuss any trial specific related queries before confirmation that the site initiation has been successfully completed.

The site initiation presentation slides can be used as a further training aid for new starters who will work on the study to ensure training standardisation. These staff will need to confirm in the training log contained within the investigator site file that they have watched the video recorded site initiation presentation slides.

A copy of the site initiation presentations will also be provided for reference in the investigator site file.

7.6 Essential documentation

The following documentation must be submitted by the site to the CTRU prior to site activation:

- All relevant institutional approvals (e.g. local NHS permission).
- A completed authorised personnel log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately).
- Completed Site Contacts Form (with contact information for the PI, co-investigators, research/trial, pharmacy, radiography and pathology staff).
- A copy of the PI's current CV that is signed and dated.
- A copy of PI's current GCP training certificate.
- Signed PI declaration.
- Radiotherapy Quality Assurance approval.
- A signed Clinical Trial Site Agreement (model Non-commercial Agreement for UK sites) between the Sponsor and the relevant institution.
- Site Initiation Training Log

In order to minimise additional work in multiple sites opening, centres are asked wherever possible, to make every effort to manage patients for trial purposes on one central site (usually the radiotherapy site). Sites must inform the CTRU of any additional sites involved in the patient pathway. Recruiting sites which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

7.7 Site activation

Once the CTRU trial team has received all the required essential documentation, the site has received their investigator site file and the site has been initiated and the necessary documentation has been sent to the CTRU, a site activation email will be issued to the PI and other research staff by CTRU.

Sites must not approach any potential patients until they have received an activation email from CTRU.

8 Consent, recruitment and randomisation

8.1 Recruitment setting

Participants will be recruited to the trial from approximately 10-12 UK radiotherapy sites, including major Yorkshire treatment centres. Research sites will be required to have obtained local management approval, completed and passed all the required quality assurance checks and undertaken a site initiation with the CTRU prior to the start of recruitment.

8.2 Recruitment and informed consent

Patients will be approached for possible recruitment following MDT diagnosis and decision to treat. Suitability for inclusion into APHRODITE will be assessed according to the eligibility criteria for the trial. A verbal explanation of the trial and the appropriate Patient Information Sheet (PIS) will be provided by the attending medical staff (and/or the trial Clinical Research Nurse) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the trial.

Following information provision, patients will have as long as they need to consider participation, normally a minimum of 24 hours, and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The formal assessment of eligibility and informed consent may only be obtained by the Principal Investigator (PI) or an appropriate medically qualified healthcare professional. The healthcare professional must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki 1996. He/she must be fully trained in the trial according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial Authorised Personnel Log. The PI retains overall responsibility for the informed consent of participants at their research site.

Informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial which are out-with standard routine care at the participating site.

Site staff are responsible for:

- Checking that the correct (current approved) versions of the PIS and Consent Form are used.
- Checking that information on the Consent Form is complete and eligible.
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form.

- Checking that an appropriate member of staff has countersigned and dated the Consent Form to confirm that they provided information to the patient.
- 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 patient trial number to the consent form and making sufficient copies and filing the original consent form in the investigator site file, and filing a copy in the patient's medical notes.
- Giving the patient a copy of their signed Consent Form, PIS and patient contact card.
- Faxing, email or posting a copy of the signed consent form to CTRU in line with the terms of the ethically approved consent form.

The participant will be provided with a local contact point where he/she may obtain further information about the trial.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

The right of the patient to refuse consent without giving reasons will be respected. Consenting participants will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment. Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

The responsibility for treatment with chemoradiotherapy and the prescription of chemotherapy and radiotherapy ultimately remains with the PI.

After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated.

8.3 Loss of capacity following informed consent

Loss of mental capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Should this eventuality occur, this should be reported to CTRU via a

withdrawal form with no further trial procedures or data collection occurring from this point. Any data collected up to the point of withdrawal will be kept on record and used in the trial analysis. This is explicit in the written information that the participant will receive.

8.4 Eligibility screening

In order to determine the generalisability of the trial results, and for Consolidated Standards of Reporting Trials (CONSORT) requirements, participating research sites will be required to complete a screening log for all patients presenting with early stage rectal cancer and screened for eligibility for the APHRODITE trial. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Anonymised information will be collected including:

- Date screened
- Age
- Sex
- The reason for non-randomisation:
  - The reason not approached, or
  - The reason not eligible for trial participation, or
  - The reason declined if eligible

However, the right of the patient to refuse consent without giving reasons will be respected. This information will be requested from participating sites on a regular basis (at least 3 monthly) by the CTRU. Once eligibility has been confirmed, participants can then be randomised.

8.5 Randomisation

Written informed consent for entry into the trial must be obtained and eligibility must be confirmed prior to randomisation.

8.5.1 Randomisation process

Following confirmation of written informed consent and eligibility, participants will be randomised into the trial by Leeds CTRU. Patients will be randomised on a 1:2 basis to receive either standard dose CRT (SDCRT) with 50.4 Gy in 28 fractions to primary tumour and mesorectal target volume, or escalated dose CRT (EDCRT) with 50.4 Gy to mesorectal target and 62 Gy to gross tumour target volumes in 28 fractions.

A computer-generated minimisation program that incorporates a random element will be used to ensure the treatment groups are well-balanced for the following, details of which will be required at randomisation:

- T-stage (<T3 vs. T3)

- Randomising site
- Chemotherapy use (either 100% or 75% dose) vs. no chemotherapy use

Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system which can be accessed via the web or telephone. Authorisation codes and personal identification numbers (PINs), provided by the CTRU, will be required to access the randomisation system.

The Randomisation Form will be completed prior to accessing the 24-hour randomisation system.

The following information will be required at randomisation:

- Site code (assigned by CTRU) of the research site.
- Name of person making the registration/randomisation.
- Participant details, including initials and date of birth.
- Confirmation of eligibility
- Confirmation of written informed consent.
- Randomising site
- T-stage (<T3 vs. T3)
- Chemotherapy use: 100% or 75% dose, including regimen used, or no chemotherapy use

Once randomisation is complete, the system will allocate participants a unique 5 digit trial number and inform site of the randomised radiotherapy dose for that participant.

24hour Randomisation:
Telephone: 0113 343 2290
Or
Web: *https://lictr.leeds.ac.uk/webrand/*

Please ensure that the following electronic case report forms (eCRFs) are completed immediately after randomisation:

- Eligibility Checklist
- Baseline Assessment
- Randomisation

A copy of the consent form should be sent via the CTRU's secure file transfer service and the baseline questionnaire must be sent to the CTRU immediately after randomisation

9 Trial treatments

9.1 CRT treatment overview

Standard dose CRT: Radiotherapy using a dose of 50. 4 Gy is applied to the primary tumour and surrounding mesorectum using IMRT, in 28 fractions of 1.8 Gy, one fraction per day, 5 days a week. Daily image guidance is used for treatment delivery.

Concurrent chemotherapy is delivered using one of two regimens, at the discretion of the treating oncologist. The regimen used must be declared prior to randomisation on the pre-randomisation check list. No cross-over between the chemotherapy regimens should occur. The possible chemotherapy regimens are briefly (FULL DETAILS IN SECTION 9.3):

1. Capecitabine 825 mg/m² orally, twice a day (b.i.d)., on radiotherapy days only (Monday-Friday), throughout the whole course of radiotherapy or:
2. 5-Fluorouracil 350mg/m^2 plus Leucovorin (5FU/LV) once per day on radiotherapy days only, during radiotherapy fractions (treatments) 1-5 and 21-25.

Escalated dose CRT: Radiotherapy using a dose of 50.4 Gy is applied to surrounding mesorectum and 62 Gy applied to the primary tumour using synchronous integrated boost IMRT, in 28 fractions, one fraction per day, 5 days a week. Daily image guidance is used for treatment delivery.

Concurrent chemotherapy is delivered using either concurrent capecitabine or 5FU/LV, as for standard dose CRT.

Elective chemotherapy dose reduction or omission

If the treating team feel that the patient is not fit enough to receive the full (100%) dose of concurrent capecitabine or 5FU/LV, because of specific co-morbidities, or general frailty, then there are the options either to treat with concurrent capecitabine or 5FU/LV chemotherapy at 75% dose, or to omit the chemotherapy altogether and treat with radiotherapy alone. The intended chemotherapy treatment option must be declared for each individual patient PRIOR to randomisation.

9.2 Radiotherapy

The key elements of the radiotherapy protocol will be outlined in this section, but detailed radiotherapy guidelines are provided in a separate document (APHRODITE Radiotherapy Guidelines), which can be accessed via the website www.rttrialsqa.org.uk.

Investigators are required to follow the detailed instructions in the guidance document. Any centres wishing to participate in this study will comply with the defined Radiotherapy Quality Assurance (RTTQA) guidelines summarised below and detailed in the Radiotherapy Guidelines.

All patients are to be treated using intensity modulated radiotherapy (IMRT, which may include arc therapy techniques).

9.2.1 Imaging for treatment planning

It is recommended that appropriate immobilisation and a scan/treatment position is used which the site is familiar with. It is strongly recommended to scan and treat in the supine position.

For the planning CT scan, a maximum slice thickness of 3 mm is mandatory, as small tumours may be very hard to visualize with larger slice thickness. The use of intravenous and oral contrast is not required, but can be used if individual centres wish to do so. The Radiotherapy Guidelines provides detailed guidance regarding rectal filling management for optimal reproduction of the planning anatomy for daily treatment.

Patients with artificial hips can be treated on trial, as long as the primary tumour can be identified on treatment plan imaging, if needed with the assistance of diagnostic and/or treatment planning MRI (see below).

9.2.2 Treatment plan outlining – target volume and organ at risk (OAR) delineation

All target volume and OAR nomenclature follows the recommendations in the American Association of Physicists in Medicine (AAPM) Task Group 263 Report 263. It is mandatory that this nomenclature is adhered to. Diagnostic and/or planning MRI scan images must be available during delineation for side-by-side comparison.

The volumes listed below must all be outlined (with the exception of PTV_Opt in the standard dose arm). Diagnostic and/or planning MRI images must be available during delineation for side-by-side comparison, to aid both primary tumour and mesorectum outlining. It is strongly recommended to have radiology assistance for identification and outlining of the primary tumour on the treatment planning imaging. Detailed illustrations and examples to guide outlining are available in the Radiotherapy Guidelines.

Table 9.1 Treatment Planning volumes

GTVp	Primary tumour; i.e. all macroscopic tumour on relevant CT slices. Only involved areas of rectal wall should be included (i.e. do not routinely encompass the full circumference of the rectum at involved levels). Rectal faecal contents are not to be included.
CTV	Nodal clinical target volume, consisting of the mesorectum considered at risk of lymph node involvement. Detailed definitions are available in the Radiotherapy Guidelines, but note specifically: • While the superior limit is defined as the S2/3 interspace, a minimum of 2 cm is required from the superior limit of the GTVp to the CTV. (In superiorly placed tumours, this may require an extension of the CTV above the S2/3 interspace to achieve the 2 cm margin.) • The inferior limit is 2 cm inferior to the inferior limit of the GTVp. However, in low tumours, where a 2 cm margin extends below the end of the mesorectum and into the anal canal, this margin is reduced, to no less than 1 cm.
PTVp	The primary tumour planning target volume. Consists of the GTVp plus an appropriate margin taking into account changes over time in patient geometry and internal organ movement. Treatment margins depend on specific on-treatment image guidance protocols as well as local protocols for organ motion management. See the Radiotherapy Guidelines for details of minimum margin requirements. Note that PTVp must be outlined for all patients (both treatment arms).
PTV	The mesorectal (nodal) planning target volume. Consists of the CTV plus an appropriate margin taking into account changes over time in the patient geometry and internal organ movement. See the Radiotherapy Guidelines for details of minimum margin requirements.
PTV_Opt	For reporting purposes in the high dose escalation arm alone, a separate structure representing PTV outside PTVp should be created. This is done by subtracting PTVp, with an additional 5mm margin, from PTV.
Spc_Bowel (Bowel cavity)	Consists of the potential bowel cavity volume, including 2 cm above the superior extent of the PTV. This includes the abdominal contents excluding major vasculature, muscles and bones, as well as other pelvic organs (e.g. bladder, prostate, vagina, uterus). The bowel cavity is not

	delineated in inferior axial slices where there is no visible small bowel or colon.
Bladder	Entire bladder including bladder wall.
Femur_Head_L & Femur_Head_R (Left & right femoral heads)	Femoral heads, contoured as two separate volumes (left and right) to the most inferior extent including the lesser trochanter.

9.2.3 Radiotherapy treatment planning

Treatment planning must be based on inverse planning; either IMRT, VMAT (arc therapy) or similar techniques. This should be delivered using megavoltage photon beams, with recommended energies of ≥ 6 MV. Dose calculation should use a modern "type B" algorithm, taking tissue inhomogeneity and lateral electron transport into account.

9.2.4 Target dose prescriptions

All doses are prescribed as target absorbed doses according to International Commission on Radiation Units (ICRU) guidelines.

Standard dose arm: A total dose of 50.4 Gy in 28 daily fractions should be delivered to the PTV, over a total time of 5 weeks, treating 5 days per week, 1 fraction per day, using 1.80 Gy per fraction.

Dose escalation arm: A total dose of 62 Gy in 28 daily fractions should be delivered to the PTVp and a total dose of 50.4 Gy in 28 daily fractions to the PTV, over a total time of 5 weeks, treating 5 days per week, 1 fraction per day, using 2.21 Gy per fraction for the PTVp and 1.80 Gy per fraction for the PTV.

Specific target dose constraints for the two treatment arms can be found in the Radiotherapy Guidelines.

There are no mandatory OAR dose constraints, but a set of optimal objectives for dose planning are provided for bowel cavity, bladder and femoral heads. These must be considered during treatment planning. Please see the Radiotherapy Guidelines for details.

9.2.5 Radiotherapy delivery and on-treatment image guidance

Rectal cancer patients exhibit significant interfraction motion of the primary tumour as well as the mesorectum. Consequently, daily 3D imaging guidance is mandatory for all patients on trial.

Centres must use this not only to minimise setup errors (by daily correction of bony anatomy offsets), but also to review internal target motion relative to the planned volumes. There is no mandated procedure for this, but a set of suggested procedures are provided in the Radiotherapy Guidelines.

9.2.6 Unplanned interruptions in radiotherapy treatment

When an unplanned break in radiotherapy occurs (e.g. public holiday, machine breakdown), capecitabine (or 5FU/LV if it was due to be given on that day) should be interrupted for that day and then resumed on the next planned day of radiotherapy. In the above circumstances the radiotherapy prescription remains unchanged i.e. the dose prescription remains either 50.4 Gy or 62 Gy in 28 fractions, even if this is delivered over a longer treatment time. Sites are encouraged to keep the overall radiotherapy time unchanged though, e.g. by treating on weekends if necessary.

9.2.7 Radiotherapy quality assurance

The radiotherapy quality assurance (RTQA) programme for the APHRODITE trial will be designed and implemented by the UK National Radiotherapy Trials QA (RTTQA) Group. The full details of the programme will be made available on the RTTQA group website, www.rttrialsqa.org.uk.

The RT QA programme for the trial will include both pre-trial and on -trial QA. Parts of this will be aligned with the STAR-TREC RT QA programme, to avoid any overlap and to allow centres already approved for STAR-TREC to limit their RT QA work. Details are available in the Radiotherapy Guidelines.

All individual patient treatment planning data will be collected during the conduct of the trial, and will be reviewed periodically by select members of the Trial Management Group (TMG) and/or RTTQA to allow for feedback to centres as the trial progresses

9.3 Chemotherapy

Two chemotherapy schedules are permitted at the discretion of the treating oncologist. It is expected that the majority of patients will receive oral capecitabine but intravenous 5-Fluorouracil/Leucovorin (5FU/LV) is available as an option for reasons such as difficulty taking tablets. No cross-over is permitted between capecitabine and 5FU/LV.

After patients have had their last fraction of radiotherapy, they will not receive any further protocol-specified capecitabine or 5FU/LV concurrent chemotherapy.

9.3.1 Capecitabine treatment schedule

The recommended 100% starting dose of capecitabine is 825 mg/m² orally, twice a day (b.i.d), on radiotherapy days only (Monday-Friday), throughout the whole course of radiotherapy. There is no dose cap and dose banding may be used for capecitabine as per local policy.

Bloods (full blood count, urea and electrolytes, liver function tests) must be measured within 14 days of commencing chemotherapy, and be within the parameters outlined in the Eligibility Criteria (Section 6).

Capecitabine is be taken on days of radiotherapy only (usually Monday-Friday) as shown in the summary treatment schedule. Patients will self-administer their recommended dose of capecitabine orally. Since current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered within 30 minutes after finishing a meal, typically 12 hourly at 8am and 8pm.

It is recommended that the first fraction of radiotherapy should be given at least 2 hours after the commencement of the first dose of capecitabine.

During radiotherapy, all patients will have weekly full blood count, urea and electrolytes and liver function tests.

Table 9.2 APHRODITE treatment schedule

*APHRODITE summary treatment schedule

Treatment	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6		
	Days 1-7							Days 8-14							Days 15-21							Days 22-28							Days 29-35							Days 36-38		
Radio-therapy	•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•
**Capecita-bine 825 mg/m² orally bd Mon-Fri	•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•
	•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•	•	•			•	•	•
**5FU 350 mg/m²/d and leukovorin 45mg/d wks 1 and 5	•	•	•	•	•																								•	•	•	•	•					

*Regime illustrated starts on a Monday although it is permitted to start on any day Monday-Friday
**One of these regimes to be chosen prior to randomisation

- For patients where there are concerns about a patient's frailty and their overall ability to withstand chemotherapy toxicity, the treating oncologist has the discretion to lower the starting dose of capecitabine to 75% i.e. capecitabine at 620mg/m² b.i.d. (or to omit chemotherapy completely).

- If radiotherapy is not given (e.g. due to machine maintenance or public holiday), then capecitabine (or 5FU/LV if due on that day), should not be given on that day.
- For patients who have difficulty swallowing capecitabine, the tablets can be dissolved in approximately 200ml of water. By agitating the tablets for approximately 15 minutes, the tablets should dissolve. There is no stability data for any form of suspension, so the tablets should be dissolved immediately before use and the solution swallowed immediately, rinsing to ensure all of the suspension has been ingested. The solution has a very bitter taste and a fruit juice can be added to make the solution more palatable, but capecitabine should not be mixed with grapefruit juice.
- If a patient vomits after taking a dose of capecitabine, the dose should not be taken again.

9.3.2 Capecitabine toxicity and dose modification

Patients should be reviewed at least weekly during CRT, and assessed for acute toxicity using CTCAE. The main expected dose limiting toxicities of capecitabine are detailed in Section 11.3.2 . It is expected that diarrhoea, fatigue and haematological toxicities will be most commonly observed. The full list of capecitabine undesirable side effects can be found in Section 4.8 of the Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/1319/smpc. Acute toxicity will be assessed based on the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Appendix E, Section 25).

Often adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced. Any overlapping toxicity (i.e. chemotherapy or radiotherapy) should be graded based upon the worst toxicity observed. All dose reductions should be clearly documented with clear reasoning. Prompt management of ongoing grade 2 or grade 3 diarrhoea is important in order to maximise chemotherapy and radiotherapy compliance.

Appendix C (Section 25) contains the full set of guidelines for dose modification for organ function and toxicity

9.3.3 Recommendations specifically for the management of severe diarrhoea (whether receiving concurrent capecitabine CRT, concurrent 5FU CRT or radiotherapy alone)

It is particularly important to assess and monitor patients who experience diarrhoea during CRT. If admission is required, it is recommended that this is to the radiotherapy centre. If circumstances prevent this, then this guidance must be rapidly shared with the local treating team and regular contact maintained. The option of subsequent transfer to the centre should be discussed.

The site team should document a baseline assessment of stool frequency and this should be repeated once weekly at the same time as toxicity assessment (distinguishing from tenesmus/mucous discharge/wet wind).

Loperamide is recommended as the initial anti-diarrhoeal medication. Codeine phosphate up to 30 mg four times a day can be added if diarrhoea is not controlled with 16 mg loperamide per day.

Grade 3 diarrhoea

The following guidance is recommended for patients who experience grade 3 diarrhoea during concurrent chemo-radiotherapy:

- Consider admission of the patient
- Commence loperamide
- Send stool for culture and C. difficile toxin
- Commence iv fluids with regular appropriate volumetric and electrolyte assessment
- Suspend chemotherapy
- If neutropenic, commence iv antibiotics and consider Granulocyte-colony stimulating factor (G-CSF)

If grade 3 diarrhoea is not controlled to ≤ grade 1 by regular loperamide within 24 hours and patient not neutropenic:

- Commence IV broad spectrum antibiotics (including patients who are not pyrexial). The regimen used should be determined locally (an example option includes an intravenous second or third generation cephalosporin and metronidazole). The regimen used should cover likely enteric pathogens.

If grade 3 diarrhoea not controlled ≤ grade 1 by IV antibiotics and IV fluids and regular loperamide within 48 hours:

- Commence s/c octreotide – the recommended starting dose is 300µg per 24 hours by either s/c continuous infusion or s/c tds injections. The dose can be increased in accordance with British National Formulary (BNF) guidance and should be reviewed daily.
- Closely monitor serum CRP, renal function and albumin. The role of total parenteral nutrition should be discussed with the multi-disciplinary team who are responsible for this therapy and may play an important role for patients not responding well to the supportive treatments described above.

Grade 4 diarrhoea:

- By definition grade 4 diarrhoea is life-threatening. Patients developing grade 4 diarrhoea at any stage must be admitted urgently and treated with full supportive measures including fluid replacement, IV antibiotics and IV octreotide in addition to any other immediate resuscitative measures that might be deemed necessary.

Guidance regarding continuation of radiotherapy is given in

Appendix 5, Section 25. Radiotherapy should be withheld in the presence of lower abdominal peritonism (rebound tenderness in clinical examination).

9.3.4 Capecitabine compliance

Diary cards will be supplied for patients treated with Capecitabine to complete for each cycle. Patients will document when each tablet is taken and any missed doses (with reasons). If a patient misses a dose of capecitabine, sites should follow local policy and advise the patient accordingly. An overview should be recorded during treatment on each Chemoradiotherapy eCRF.

9.3.5 Treatment data collection

Trial treatment must be recorded on the MACRO Remote Data Entry (RDE) system. In addition, reasons for any dose delays, reductions or omissions or for permanent discontinuation of trial treatment must be recorded on the Chemoradiotherapy eCRF on MACRO.

The number of tablets taken will be recorded by the patient on the diary card that they complete on a daily basis, documenting any missed doses (with reasons). If a patient misses a dose of capecitabine, sites should follow local policy and advise the patient accordingly. This information will be checked in a standard outpatient's appointment. All the packaging and unused tablets must be returned by patients and returned to pharmacy for disposal according to local policy.

Capecitabine should be prescribed from commercially available stock and will not be supplied by APHRODITE. Capecitabine is a licensed product and is being used within its licensed indication. For all storage, reconstitution and formulation please refer to the most recent version of the Summary of Product Characteristics (SPC) which can be found on the Medicine Guide Website, http://emc.medicines.org.uk.

9.3.6 Dispensing and Drug Supplies

Capecitabine will be used from commercially available stock and used within its licensed indication. The current SPC should be referred to for further details on storage and preparation.

Supportive medications such as metoclopramide (for nausea) and loperamide (for diarrhoea) should be used as required.

Study medication will be dispensed at the start of treatment.

The guidelines in this protocol are in line with manufacturers recommendations at the time of writing.

9.3.7 Accountability and unused drugs

The trial pharmacist will sign a document to confirm that local hospital systems are in place to cover drug ordering, drug receipt, drug storage and dispensing, and will enable accurate traceability of all drugs used in the trial.

No special accountability arrangements (over and above what is required locally at each hospital) are required for the capecitabine commercial stock used in APHRODITE.

Unused, used or partially used stocks of capecitabine should be disposed of at site according to local policy.

9.3.8 Overdose of trial medication

A dose of capecitabine in excess of that specified according to the protocol will constitute an overdose. The decision on whether an overdose has occurred will be based upon local clinician discretion and should be managed according to standard local practice.

9.3.9 5-Fluorouracil/leucovorin (5FU/LV) treatment schedule

5FU/LV can be used as an alternative to capecitabine at the discretion of the treating oncologist. The standard (100%) regimen is as follows: Leucovorin 20mg/m^2 is delivered via a short IV push (LV dose banding or a standard flat dose for all patients can be used according to local policy). This is then immediately followed by 5FU 350mg/m^2 in 500ml of normal saline over 1 hour (there is no 5FU dose capping and 5FU dose banding can be used according to local policy). This is given once per day on radiotherapy days only, during radiotherapy fractions (treatments) 1-5 and 21-25. It is simplest if radiotherapy starts on a Monday, when 5FU/LV would be given Monday-Friday during week 1 (overall days 1-5) and Monday-Friday during week 5 (overall days 29-33). 5FU/LV should be commenced prior to radiotherapy on the days it is given. For patients where there are concerns about frailty and their overall ability

to withstand chemotherapy toxicity, the treating oncologist has the discretion to lower the starting dose of 5FU/LV to 75% i.e. 5FU at 260mg/m^2/d (keeping LV dose unchanged) (or to omit chemotherapy completely).

9.3.10 5FU/LV dose delays and dose reductions

Common and expected toxicities for FU must be checked weekly during CRT to ensure that the patient can safely be administered the drug. The main expected dose limiting toxicities of 5FU/LV are detailed in Section 11.3.2. The full list of undesirable 5FU side effects can be found in Section 4.8 of the Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/3791/smpc). Acute toxicity should be graded as per CTCAE grading (Appendix E, Section 25). Instructions for dose modifications for chemotherapy toxicities are included in Appendix C, Section 25. Often adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced. Any overlapping toxicity (i.e. chemotherapy or radiotherapy) should be graded based upon the worst toxicity observed. All dose reductions should be clearly documented with clear reasoning.

9.4 Medications outside of trial (relevant to both capecitabine and 5FU/LV)

9.4.1 Contraindicated concomitant medications with Capecitabine or 5FU

Concomitant administration of the following medications with Capecitabine or 5FU is contraindicated:

- Sorivudine (or Sorivudine analogues e.g. Brivudine) - there must be at least a 4-week period between the end of treatment with Sorivudine or its chemically related analogues and the start of CRT
- Clozapine – discontinue at least 14 days prior to the start of CRT
- Warfarin – discontinue at least 7 days prior to the start of CRT

9.4.2 Medications to be avoided with Capecitabine or 5FU

- Dipyridamol and allopurinol – concomitant use with Capecitabine or 5FU should be avoided.
- Phenytoin - patients receiving phenytoin concomitantly with Capecitabine or 5FU should be regularly monitored for increase phenytoin plasma concentrations and associated symptoms.

- Metronidazole in combination with 5FU can increase plasma concentrations of 5FU, so should be used with extreme caution. There are no reports of interaction between Capecitabine and metronidazole, however, caution is advised in its use for patients in combination therapy arm due to known interaction between 5FU and metronidazole.
- Folic Acid – concomitant use with Capecitabine should be avoided.

9.4.3 Use of anticoagulants with Capecitabine or 5FU

Altered coagulation parameters and/or bleeding have been reported in patients taking Capecitabine or 5FU concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. The mechanism of interaction is unclear. These events occur within several days and up to several months after initiating Capecitabine/5FU therapy and, in a few cases after stopping Capecitabine/5FU.

In addition, in the HERBERT trial, which examined brachytherapy boost following external beam RT in elderly or medically inoperable patients, serious grade 3 rectal bleeding was primarily observed in patients using anticoagulants (Rikjmans 2017). Therefore patients receiving oral warfarin are only eligible for APHRODITE if one of the two options listed below can be used according to clinical judgement:

- Discontinuation of warfarin at least 7 days prior to commencement of treatment and for the duration of radiotherapy/CRT (this may be reasonable when given as prophylaxis for patients with atrial fibrillation – this is a local clinician decision).

or

- Conversion from oral warfarin to low molecular weight heparin where local clinical opinion considers this an acceptable option – the change to low molecular weight heparin with discontinuation of warfarin should be made at least 7 days prior to the commencement of treatment.

Warfarin must not be commenced during CRT.

There is no reliable data to support an interaction between factor Xa inhibitors such a rivaroxaban and apixaban, and capecitabine or 5FU/LV. There is therefore no requirement for these to be stopped during CRT.

9.4.4 Further post protocol defined anti-cancer treatment

No specific recommendations are made regarding further post protocol defined anti-cancer treatment. After primary endpoint assessment, treatment should be as per local policy. However, APHRODITE assessments should continue as planned.

9.5 Withdrawal of treatment

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. All participants withdrawn from treatment or prescribed alternative treatment will still attend for follow-up assessments unless unwilling to do so and eCRFs or paper CRFs will continue to be completed.

The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal Request eCRF, in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

It should be made clear to any participant specifically withdrawing consent for further data collection that further data pertaining to safety will continue to be collected, for example the outcome of an event that was reported prior to withdrawal, and will be included in any safety analysis. In addition it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future.

10 Assessments

10.1 Prior to randomisation in APHRODITE

The following investigations and assessments must be carried out prior to randomisation, and may, if part of standard clinical care, be used to establish eligibility:

No specific time limit:

- Flexible sigmoidoscopy
- Diagnostic biopsy

Within 63 days prior to randomisation

- CT scan (chest/abdomen/pelvis)

Within 42 days prior to randomisation:

- MRI scan (pelvis)

Within 14 days prior to randomisation:

- ECOG Performance status
- Vital signs, height, weight
- Pregnancy test (if woman of child bearing potential) as per local practice
- Full blood count, Urea and Electrolytes (U&Es), Liver Function Tests (LFTs)
- Electrocardiogram (ECG)
- Medical history
- Physical examination
- Digital rectal examination[1]
- Baseline CTCAE symptom scores
- Completion of the baseline QoL questionnaires by the patient

10.2 Pre-treatment (≤10 day of treatment)

- Performance status
- Full blood count, Urea and Electrolytes (U&Es), Liver Function Tests (LFTs)
- Review of potential contraindicated medications

Note, however, that investigations / assessments carried out at baseline (pre-randomisation) do not need to be repeated if done within 10 days of radiotherapy treatment start.

[1] Please note, DRE should be within 14 days prior to randomisation if possible. However, if the baseline DRE is more than 14 days deviation is permitted, but must be discussed with CTRU prior to randomisation.

10.3 Weekly assessments during CRT

Participants will be assessed clinically for symptoms and toxicity each week of CRT treatment, including full blood count and biochemistry. Toxicities will be assessed based on the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0). A copy of NCI-CTCAE is provided in the Investigator Site File.

Details of chemoradiotherapy treatment will be collected on a weekly basis by completing the Chemoradiotherapy eCRF. Data collected will include (but will not be limited to):

- Date treatment started and ended
- Weekly number of fractions and weekly dose of radiotherapy given
- Details of any interruptions to radiotherapy, including reason
- Chemotherapy details (type of any dose delays or dose reductions that have occurred, and reason for these)
- Acute toxicity scores for adverse events related to CRT using CTCAE

10.4 End of treatment

A telephone-based assessment will be carried out two weeks following completion of CRT, i.e. at approximately 7.5 weeks following the start of CRT, to assess CTCAE toxicity and performance status. This can be done by a trial nurse.

The End of Treatment eCRF and the 2 week post completion of CRT Telephone Follow-up eCRF must be entered on the RDE system within 7 working days of each assessment.

10.5 Follow-up assessments

Follow-up visits will be as follows (from the start of CRT): 3, 6, 9, 12 and 24 months. Details of assessments are included in Section 10.

Follow-up data will be collected at these time points by completing the relevant eCRF. At follow-up visits, data will include, but will not be limited, to the following:

- Patient status
- Presence and details of stoma
- Details of any further cancer-specific treatment such as systemic anti-cancer treatment (SACT) or surgery.
- Late toxicity using selected CTCAE measures
- Disease progression

Trial specific follow-up assessments should, if at all possible, be conducted irrespective of any subsequent rectal cancer progression or recurrence or any new primary cancers.

The treating team are encouraged to decide on an individual patient basis whether additional disease surveillance assessments are needed in the follow-up period, over and above those mandated in the APHRODITE protocol. This is especially relevant to two clinical scenarios:

1. In the case of patients with an 'uncertain cCR' at 6 months (where the criteria for a cCR are fulfilled but there is in addition superficial ulceration), teams may decide to perform additional assessments to those in the protocol to help decide whether such patients have residual disease or not. For these patients centres will be specifically asked to report on the eCRF at 12 months post the start of treatment, whether with an additional six months of follow-up it has been possible to determine if the superficial ulceration was due to persistent tumour or not.

2. For patients who achieve the primary endpoint of a cCR at 6 months, and who have good performance status and did not originally have surgery because of a marked patient desire to avoid surgery and a stoma, more intensive surveillance of local tumour control may be deemed appropriate, aiming to offer such patients salvage surgery if they subsequently develop local tumour recurrence.

Clinical management beyond 24 months is at the discretion of the local treating team.

10.6 Baseline and follow-up MRI

Imaging using MRI is of importance in APHRODITE because it partly defines the primary end point. A separate document 'APHRODITE MRI Guidelines' contains details of this aspect.

MRI scans of the first 2 patients from each site will be reviewed centrally. Initially, the images received from various sites will be quality checked to ensure all images have been appropriately anonymised. The TMG radiologists will ensure the inclusion criteria have been met on the baseline scan and that the response at 3 and 6 months has been correctly reported. Further review of post treatment MRI scans may be performed in batches.

The baseline, 3m and 6m MRIs use the same imaging protocol, adhering to consistent parameters, including diffusion weighted imaging.

Reporting of MRI scans at 3m and 6m will include MRI tumour regression grade (mrTRG) (see the document 'APHRODITE MRI Guidelines' for examples).

While not mandated on trial, the treating team are encouraged to assess on an individual patient basis the need for additional surveillance MRIs, e.g. for patients with an 'uncertain cCR' at 6 months, or for those with a cCR at 6 months and who are of good performance status and may be offered salvage surgery if they relapse locally.

Table 10.1 MRI Tumour regression grading (mrTRG) scores on post-treatment MRI

Grade	Description
Grade 1	Complete radiological response (linear scar only), no evidence of treated tumour
Grade 2	Excellent response (dense low signal post treatment fibrotic change in the site of the previous tumour) and no obvious tumour signal
Grade 3	Moderate response (mixed fibrosis and indeterminate heterogeneous signal intensity) suspicious for residual tumour
Grade 4	Minimal response (mostly tumour, minimal fibrosis/mucinous degeneration)
Grade 5	No response in the primary tumour or frank tumour progression

10.7 Baseline and follow-up rectal endoscopy

Endoscopic examination of tumour response is of importance in APHRODITE because it partly defines the primary endpoint. A separate document '**APHRODITE Endoscopy Guidelines**' contains details and guidelines with regard to this aspect.

Anonymised pre-treatment, 3 month and 6 month post-treatment endoscopic photographs will be collated for the first 2 patients from each site and reviewed centrally. Ideally these will be sent electronically to the coordinating centre. Initially, the images received from various sites will be quality checked to ensure all images have been appropriately anonymised. The TMG endoscopic specialists will ensure that the response at 3 and 6 months has been correctly reported and this assessment will be fed back to sites promptly. Further review of post treatment endoscopies may be performed in batches.

While not mandated on trial, the treating team are encouraged to assess on an individual patient basis the need for additional surveillance endoscopies e.g. for patients with an 'uncertain cCR' at 6 months, to determine if they have persistent tumour or not, or for patients who achieve a cCR at 6 months and who have good performance status and on review may be eligible for salvage surgery if their disease recurs locally.

10.8 Assessment of efficacy / primary endpoint

All patients will be assessed for whether or not they have achieved a clinical complete response at 3 and 6 months post start of treatment. The 6 month assessment will inform the trial's primary endpoint. Response to treatment will be assessed via clinical examination, endoscopy (flexible sigmoidoscopy) and imaging using pelvic MRI, with a declaration of cCR based on the combined assessment not indicating any remaining active tumour (**Section 12.1**).

10.9 Deaths

All deaths occurring from the date of randomisation to the end of follow-up must be recorded on the Notification of Death eCRF on the RDE system within 7 days of the site team becoming aware of the death. It is important that this is completed promptly so that any QoL questionnaire reminders sent by CTRU are stopped. Data collected will include (but may not be limited to):

- Date of death
- Cause of death

10.10 Pregnancies

All pregnancies and suspected pregnancies in a trial participant, or their partner, occurring from the date of randomisation to six months after completion of CRT treatment must be reported to the CTRU within 24 hours of the site becoming aware. All protocol treatment must be stopped immediately if a pregnancy in a female participant occurs or is suspected.

The CTRU will report all pregnancies occurring during treatment to the Sponsor along with any follow-up information.

10.11 End of trial

The end of the trial is defined as the date of the collection of the last participant's data item. All evaluable trial participants will be followed up until this point. Follow-up data will be collected from sites until two years post start of treatment.

10.12 Trial assessments and data collection

Assessments will be entered electronically via Remote Data Entry (RDE) onto electronic case report forms (eCRFs), using the MACRO programme which will be managed by the CTRU. Access to the RDE system will be provided by the University of Leeds following site being authorised to open to recruitment; guidance on RDE and completing eCRFs will be provided.

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File, (ISF)), which will be provided by the CTRU, and keep copies of any completed paper Case Report Forms (CRFs) for the trial. The paper CRFs and participant-completed questionnaires will contain the participant's unique trial number, date of birth, and initials.

It is the responsibility of the site staff to ensure the ISF is properly maintained during the duration of the trial.

10.13 Electronic Case Report Forms (eCRFs) and paper Case Report Forms (CRFs)

Data will be recorded by site research staff on trial-specific eCRFs, which will be provided by CTRU on a trial-specific database. All eCRFs must be completed within 28 days of the data collection time points detailed in Section 10. Some of data will still be collected using paper case report forms (CRFs), which will be provided by CTRU in the form of an electronic booklet.

A number of (e)CRFs which require expedited reporting to the CTRU, will be collected within the time points specified below:

- A copy of the consent form must be sent via the CTRU's Secure File Transfer Service (SFTS) at the time of consent.
- Paper SAR and RUSAE CRFs must be reported to CTRU within 24 hours of becoming aware of the event, this may be done by fax or sending a copy via the SFTS and notifying CTRU by email (Aphrodite@leeds.ac.uk).
- Paper protocol violation CRFs must be reported to CTRU within 7 days of becoming aware of the event. This may be done by fax or by sending a copy via the SFTS and notifying CTRU by email (Aphrodite@leeds.ac.uk).
- Notification of Pregnancy eCRFs must be entered within 24 hours of the site becoming aware and notifying CTRU by email (Aphrodite@leeds.ac.uk).
- Any Notification of Death eCRFs must be entered within 7 days of the site team becoming aware and notifying CTRU by email (Aphrodite@leeds.ac.uk).
- Any Withdrawal Request eCRFs must be entered within 7 days of the date of withdrawal.
- End of treatment eCRFs must be entered within 7 days of completion of the end of chemoradiotherapy treatment or failure to start treatment.

It is the responsibility of staff at participating sites to obliterate all personal identifiable data on any hospital reports, letters, etc., prior to sending to CTRU. Such records should only include the trial number, initials and date of birth to identify the participant. The exception to this is the participant consent form where the participant name and signature must not be obliterated.

Following receipt of the completed eCRFs, the CTRU will contact sites on a regular basis to resolve any missing or discrepant data.

RDE/ eCRFs must only be completed by personnel authorised to do so by the Principal Investigator, as recorded on the trial-specific Authorised Personnel Log (APL). Login details will be provided for these personnel only and should not be shared with others.

10.14 Patient reported Outcome Measures (PROMs) including Quality of Life (QoL)

PROMs assessments will take place at baseline, end of CRT treatment (5.5 weeks), and then 3, 6, 9, 12 and 24 months post-start of CRT. Questionnaires will be completed by participants on attendance at the scheduled outpatient appointments, prior to being seen in clinic. Questionnaires should be completed independently by the participant. The completed questionnaires will then be sent promptly to Leeds CTRU.

10.14.1 PROMs questionnaires to be completed

Questionnaires to be completed include the EORTC QLQ-C30, CR29, with additional relevant items, and LARS (Low Anterior Resection Syndrome). The EORTC QLQ-C30 is a validated multi-dimensional tool for assessing QoL in cancer patients, formed of 30 questions addressing aspects of patients' physical and mental functioning and symptoms as well as their overall health and quality of life. The QLQ-CR29 is a validated, disease specific questionnaire for colorectal cancer patients. Additional relevant items from the EORTC QLQ Item library will be included to cover aspects of organ preservation not covered in the existing modules. The validated LARS is a short 5-item questionnaire covering bowel symptoms.

10.14.2 PROMs questionnaires at baseline and end of CRT

Research staff will provide the participant with the baseline questionnaire pack in clinic, prior to treatment. Participants will be asked to complete the baseline and end of CRT questionnaires in clinic. Once completed the research staff will then promptly send the questionnaire to Leeds CTRU.

10.14.3 Post-treatment PROMs questionnaires

Questionnaires at 3m, 6m, 9m, 12m and 24m from CRT start will be completed by the participant on attendance at the outpatient department, prior to being assessed by their medical team. The completed questionnaires will then be sent promptly to Leeds CTRU.

The timing of assessments is summarised in tables on the following pages.

10.15 Tumour sample collection

A separate Aphrodite Translational Manual out with this protocol is available for participating centres, containing full instructions for labelling, packaging and sending slides, blocks and reports.

In summary, the following samples should be collected and forwarded for central review:

1. Pre-treatment glass H&E-stained diagnostic biopsy slide(s)
2. Pre-treatment diagnostic biopsy report

The following samples should be collected and forwarded for future translational research:

3. Pre-treatment diagnostic biopsy FFPE block(s)

Materials will be sent to the APHRODITE tissue collection for the attention of Dr Nick West at St. James's University Hospital (full instructions are in the Aphrodite Translational Manual).

10.16 Baseline and on-treatment assessments

Table 10.2 Baseline and on-treatment assessments

	Prior to patient consent	Baseline (Prior to randomisation)	Baseline (prior to randomisation but after consent)	Pre-treatment (≤10 days of treatment)	On treat. 1w	On treat. 2w	On treat. 3w	On treat. 4w	On treat. 5w	End of treat. (5.5w)	2w post CRT (7.5w)
Informed consent		**X**									
Histopathology	**X**										
Performance status[a]	**X**			**X**						**X**	**X** (phone)
Bloods[b]	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Pregnancy screening	**X**										
ECG			**X**								
MRI (pelvis)[c]	**X**										
CT (chest, abdo, pelvis)[d]	**X**										
Flexible sigmoidoscopy	**X**										
Digital rectal examination[e]	**X**										
Clinical assessment	**X**				**X**	**X**	**X**	**X**	**X**	**X**	
Baseline CTCAE symptoms			**X**								
Acute toxicity[f](CTCAE)					**X**	**X**	**X**	**X**	**X**	**X**	**X** (phone)
PROMs[g]			**X**							**X**	

a. ECOG performance status to be used (Appendix A, Section 25); b. Full blood count, urea and electrolytes, liver function tests; c. High resolution MRI pelvis to be done within 42 days of randomisation; d. CT scan thorax, abdomen, pelvis to be done within 63 days of randomisation; e. DRE to be done within 14 days of randomisation if possible. If more than 14 days must be discussed with CTRU prior to randomisation; f. NIH CTCAE v5.0; g. EORTC QLQ C30, EORTC CR29 and LARS score.

10.17 Follow-up assessments

Table 10.3 Follow-up assessments*

	All timed post start of CRT				
	3 months	**6 months**	**9 months**	**12 months**	**24 months**
Performance status[a]	**X**	**X**	**X**	**X**	**X**
MRI (pelvis)[b]	**X**	**X**	(follow local protocol for active surveillance – no trial specific scans)		
CT (chest, abdomen, pelvis)	(follow standard schedule for colorectal cancer patients – no trial specific scans)				
Flexible sigmoidoscopy	**X**	**X**		**X**	
Digital rectal examination	**X**	**X**	**X**	**X**	**X**
Clinical assessment	**X**	**X**	**X**	**X**	**X**
Late toxicity[c]	**X**	**X**	**X**	**X**	**X**
PROMs[d]	**X**	**X**	**X**	**X**	**X**

*Additional assessments including digital rectal examinations, rectal endoscopies and pelvic MRI scans may be carried out at the treating team's discretion according to the judged clinical need, for example an 'uncertain cCR' at 6 months, or a cCR at 6 months in good performance status patients who may be eligible for salvage surgery if their cancer recurs locally.

a. ECOG performance status to be used (Appendix, Section 25);
b. High resolution MRI pelvis
c. Selected measures from NIH CTCAE v5.0;
d. EORTC QLQ C30, EORTC CR29 and LARS score

11 Safety Reporting

11.1 General definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with the treatment.

11.1.2 Adverse Reaction (AR)

Adverse reactions (ARs) are all untoward and unintended responses to the trial treatment. This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

Trial treatment in APHRODITE is defined as CRT or RT.

11.1.3 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Consists of a congenital anomaly or birth defect.
- Is otherwise considered medically significant by the Investigator.

11.1.4 Serious Adverse Reaction (SAR)

A Serious Adverse Reaction (SAR) is an SAE deemed to have been related to the trial treatment. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol Section 11.4 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

11.1.5 Related Unexpected Serious Adverse Event (RUSAE)

A serious adverse reaction which is related and unexpected (termed Related Unexpected Serious Adverse Event, or RUSAE) will require expedited reporting (see section 11.3, 11.3.3) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms related and unexpected as:

- Related: that is, it resulted from administration of any research procedures.
- Unexpected: that is, the type of event that in the opinion of the investigator is not considered expected.

When determining whether an SAR is expected or not, please refer to the relevant version of the Summary of Product Characteristics that is used locally.

11.2 Reporting requirements for ARs

Non-serious AEs which have no causal relationship with trial treatment will not be collected in this trial, but must still be recorded in the participant's medical notes.

Information about all ARs, whether volunteered by the participant, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the relevant eCRF and will be evaluated for duration and intensity according to the current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)– Appendix E, Section 25. Information on all ARs will be collected weekly during CRT and up to 2 weeks beyond (7.5 week assessment from start of CRT), and selected late toxicities during follow-up, according to the schedule of assessments illustrated in Section 10.3.

11.3 Recording and reporting SARs and RUSAEs

11.3.1 Events classed as expected SARs

Examples of events which will be classed as expected SARs within this trial and therefore will not be reportable as RUSAEs are given below. This is not intended to be an exhaustive list, therefore when determining whether an SAR is expected or not, please always refer to the relevant SPC that is used locally.

11.3.2 Main expected SARs related to Capecitabine/5FU/radiotherapy

Full list of 5FU undesirable side effects can be found in Section 4.8 of the Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/3791/smpc

Table 11.1 SARs related to Capecitabine / 5FU / radiotherapy

	Capecitabine	5-Fluorouracil	Radiotherapy
Blood & Lymphatic System			
Anaemia	✓	✓	✓
Leucopenia	✓	✓	
Neutropenia	✓	✓	✓
Febrile neutropenia	✓		
Pancytopenia		✓	
Thrombocytopenia	✓	✓	✓
Cardiac			
Chest pain	✓	✓	
Tachycardia	✓	✓	
ECG changes	✓	✓	
Dermatology/Skin			
Alopecia	✓	✓	
Hand-foot syndrome or palmar-plantar erythrodysesthaesia	✓	✓	
Nail changes	✓		
Dermatitis			✓
Skin erythema/ulceration			✓
Gastrointestinal			
Abdominal pain	✓		
Anorexia	✓		
Constipation	✓		✓
Diarrhoea	✓	✓	✓
Dyspepsia	✓		
Nausea	✓	✓	✓
Stomatitis	✓	✓	
Mucositis		✓	
Vomiting	✓	✓	
Ano-proctitis			✓
Proctalgia			✓
Rectal bleeding			✓
Rectal stenosis			✓
Rectal urgency			✓
Faecal incontinence			✓

Infections/Infestations			
Infections		✓	✓
Musculoskeletal			
Arthralgia	✓		
Myalgia	✓		
Ataxia		✓	
Dysgeusia	✓		
Dysaesthesia	✓		
Headache	✓		
Paraesthesia	✓		
Peripheral neuropathy	✓		
Bone fracture			✓
Ocular/Visual			
Conjunctivitis		✓	
Watery eye (epiphora, tearing)	✓		
Vascular			
Lower limb oedema	✓		
Hypertension	✓		
Embolism and thrombosis	✓		
Renal and Urinary			
Dysuria			✓
Haematuria			✓
Urinary urgency			✓
Incontinence			✓
General Symptoms			
Asthenia	✓		
Fever		✓	
Fatigue	✓	✓	✓
Lethargy	✓		

11.3.3 Reporting and recording requirements for SARs and RUSAEs

All SARs and RUSAEs occurring during the weeks of CRT treatment and up to 2 weeks beyond (approximately 7.5 week assessment from start of CRT), must be recorded on the SAR or RUSAE paper CRF and faxed, or emailed to the CTRU within 24 hours of the trial site team becoming aware of the event. Selected late toxicities occurring during follow-up must also be recorded and reported as above.

For each SAR and RUSAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed, emailed or posted to the CTRU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Assessment of expectedness must be made by an authorised medically qualified person. If such as person is unavailable, initial reports without expectedness assessment should be faxed, emailed or posted to the CTRU by a healthcare professional within 24 hours but must be followed up by medical assessment as soon as possible thereafter.

Once all resulting queries have been resolved, the CTRU will request the original form should also be posted to the CTRU and a copy to be retained on site.

All SARs assigned by the PI or delegate (or following Chief Investigator review) as unexpected will be classified as RUSAE and will be subject to expedited reporting to the Sponsor and the REC by the CTRU on behalf of the Chief Investigator in accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs) and Sponsor requirements.

11.3.4 Serious Adverse Events of Interest (SAEoI)

The following serious events occurring during the weeks of CRT treatment must be reported to the CTRU within 24 hours of the trial site team becoming aware of the event. They should be reported in the same way as SARs.

1. Angina / myocardial infarction
2. Pulmonary embolism
3. Serious skin reactions (Toxic Epidermal Necrolysis (TEN), Stevens Johnson Syndrome (SJS))

11.4 Responsibilities

Principal Investigator (PI)

1. Checking for ARs when participants attend for treatment.
2. Using medical judgement in assigning seriousness and expectedness using the relevant Summary of Product Characteristics used locally.
3. Ensuring that all SARs (including RUSAEs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up

information as soon as available. Ensuring that SARs (including RUSAEs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.

4. Ensuring that ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

Chief Investigators (CI) / delegate or independent clinical reviewer

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness and expectedness of SARs where it has not been possible to obtain local medical assessment.
3. Immediate review of all RUSAEs.
4. Review of specific SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

CTRU

1. Central data collection and verification of ARs, SARs and RUSAEs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of RUSAEs to the REC and Sponsor within required timelines.
5. Notifying Investigators of RUSAEs that occur within the trial which compromise participant safety.
7. Preparing annual safety reports for the REC.

Trial Management Group (TMG)

In accordance with the Trial Terms of Reference for the TMG will provide clinical and practical advice on trial related matters. The TMG is accountable to the TSC and DMEC and are responsible to escalate concerns to these committees.

Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing blinded safety data and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

12 Endpoints

12.1 Primary endpoint:

- Clinical complete response at 6 months from the start of CRT

Participants will be assessed for their primary endpoint at 6 months post start of treatment. Response to treatment will be assessed via clinical examination, endoscopy and imaging using pelvic MRI in accordance with the Tumour Regression Grading (mrTRG) system.

Clinical complete response (cCR) will be defined as:

1. No evidence of either mucosal tumour or submucosal swelling on white light endoscopy. A flat white scar remains, with or without telangiectasia.
2. No palpable tumour upon digital rectal examination (DRE).
3. High resolution pelvic MRI scanning shows either a linear scar only, or dense fibrosis with no obvious tumour signal (mrTRG 1 or 2).

Every effort should be made to ensure that trimodality assessment of response occurs at 3 and 6 months (endoscopy, DRE, MRI). However, in the unusual circumstance when this might not be possible for a specific patient, confirmation of a cCR should always include rectal endoscopy. If one of either DRE or MRI cannot be assessed for a specific patient, then confirmation of cCR may still occur based on the endoscopy plus either DRE (if tumour was originally palpable pre-treatment), or pelvic MRI.

12.2 Secondary endpoints

12.2.1 Acute toxicity

Clinician assessment of acute toxicities will take place during each week of treatment and up to 2 weeks post-end of treatment. They will be evaluated according to the current NCI-CTCAE criteria and include all ARs, SARs and RUSAEs.

12.2.2 Compliance with treatment

Data on the treatment participants receive will be collected weekly. Compliance to the treatment will be assessed and include adherence to both the radiotherapy and if received adjuvant chemotherapy.

Information will be recorded on the total dose of radiotherapy received (dose and fractions), the overall treatment time (i.e. start and end date), details of any interruptions to the radiotherapy and the reasons for these interruptions (i.e. toxicity or other). Adherence to the radiotherapy schedule will be defined as a participant that had completed their scheduled course of radiotherapy with no more than three treatment days of interruptions due to toxicity.

For those participants receiving chemotherapy, information will also be recorded on any treatment modifications, including delays, omissions or reductions, and their associated reasons.

12.2.3 Late toxicity

The late toxicity period will start after the 2 week post-end of treatment telephone assessment until the final follow-up visit at 24 months post-start of treatment. Clinician assessment of late toxicity will take place during each of the follow-up visits and will be recorded at 3, 6, 9, 12 and 24 months post start of treatment. post the end of treatment up until the final follow-up visit at 24 months post-start of treatment. The toxicities will be evaluated using selected CTCAE measures and include all ARs, SARs and RUSAEs.

12.2.4 PROMs

PROMs data will be captured via the EORTC QLQ-C30, QLQ-CR29 and LARS questionnaires and additional EORTC item bank questions. PROMs will be requested at baseline, end of treatment, and 3, 6, 9, 12 and 24 months post the start of treatment.

12.2.5 Stoma rate

Stoma data will be collected at standard follow-up visits. Stoma rates will be presented and analysed as a time-to-event outcome i.e. the time from randomisation to the fashioning of a stoma.

12.2.6 Overall survival

Overall survival (OS) is defined as the time from randomisation to the date of death from any cause. Survival data will be collected at standard follow-up visits.

13 Statistical Considerations

13.1 Sample size and planned recruitment rates

Sample size: 104 patient and planned recruitment rates over 2 years.

Based on a cCR rate of 35% in the control arm (Dossa 2017), this trial is powered on detecting an absolute difference of 20% (to 55%) between the control and experimental arms in terms of 6 month cCR rates. With 80% power and a 1-sided type 1 error rate of 20%, 104 patients are required (incorporating a 5% loss to follow-up rate). With a 1:2 allocation ratio, approximately 34 patients will be randomised to the control arm (standard dose CRT), and 70 to the experimental arm (escalated dose CRT). This calculation is based on a two-group chi-squared test (continuity corrected) of equal proportions allowing for a formal statistical comparison between the two arms.

Justification of assumptions made within the sample size calculation are as follows:

13.1.1 Inflated type 1 error (significance level) and 1-sided test

An inflated type 1 error rate of 20% is considered appropriate within the phase II setting where the aim is to show sufficient preliminary evidence of activity (Rubinstein 2005, Korn 2012). This is favoured, in combination with a concurrent control arm, over the use of a single arm trial with reduced type I error, as this enables direct comparison and avoids the risk of incorrect decision making due to uncertain historical control data (Sargent 2009). A 1-sided alpha is used as standard for phase II trials, as we would only progress to further studies if an increased cCR rate is observed in the experimental arm.

13.1.2 Control arm rate and clinically meaningful difference

The cCR rate of 35% in the control arm is based on published series of CRT trials (Dossa 2017) and adjusted to take account of the early rectal cancer case mix for this study. Previous data suggests that we may observe a difference as great as 25%, or even greater, in cCR rate between the two arms (in favour of the experimental arm) (Appelt 2013, Appelt and Jakobsen 2015, Appelt 2015). Therefore 20% was chosen as a conservative estimate for this difference to ensure that the trial is adequately powered, and will produce an informative result, noting particularly that 20% would be a clinically meaningful difference and one which would warrant further testing of the experimental strategy.

13.1.3 Planned recruitment rate:

We anticipate that with approximately 10-12 radiotherapy sites and their associated cancer units recruiting patients, 40 will be recruited in year 1 and 64 in year 2.

14 Statistical Analysis

14.1 General considerations

Statistical analysis is the responsibility of the CTRU Statisticians. The analysis plan detailed below provides an overview of the analyses to be performed. A separate and fully detailed statistical analysis plan (SAP) will be written before any analyses are undertaken and in accordance with CTRU standard operating procedures.

Analysis of the primary and secondary endpoints will be performed on a modified intention-to-treat (MITT) basis, unless specified otherwise within the SAP. The MITT population is defined as all participants randomised, who received at least one dose of trial treatment on study. The group divide, for all analysis and summaries, is the treatment group each participant was randomised to regardless of ineligibility and non-compliance or withdrawal from the study. The MITT was considered appropriate in this phase II setting focused on an efficacy signal.

14.2 Frequency of analysis

The primary endpoint analysis will take place once the final participant has reached their primary endpoint, i.e. 6 months post start of treatment, and once all data have been received and cleaned.

Analysis of the secondary endpoints will take place once the final participant has been followed-up to 24 months post randomisation.

There are no formal interim analyses planned within this trial.

14.3 Primary endpoint analysis

The final evaluation of the APHRODITE trial, as to whether radiotherapy dose escalation increases the cCR rate compared with standard dose CRT, will be based on the primary analysis using the standard definition of cCR, as defined in Section 12.1.

A multivariable logistic regression model, adjusted for the minimisation factors, will be used to compare 6 month post-start of treatment cCR rates between the treatment arms for the proportion of participants who have achieved a cCR. Significance testing will be 1-sided and at the 20% level. The treatment effect will be presented as an odds ratio with 1-sided 80% lower confidence limit.

The proportion of participants within each clinical response status, 6 months post-start of treatment, will be reported. The proportion of participants achieving a cCR at 6 months post start of treatment and the associated 60% confidence intervals (CIs) (2-sided) will be presented overall and by treatment arm, and compared using a chi-squared test.

Sensitivity analysis

A cCR as defined in Section 12.1 is based on clinical experience with standard dose radiotherapy. Consideration was given as to whether the presence of superficial mucosal ulcerations should also be considered in the definition of a cCR i.e. patients classed as having an 'uncertain cCR'. There is a concern that a higher dose of radiotherapy may induce more ulcerations, and slower healing ulcerations, therefore potentially biasing the primary endpoint using the standard definition against the escalated dose arm. In order to help inform future research on higher dose radiotherapy trials, a sensitivity analysis will be conducted whereby the primary endpoint analysis will be repeated, using a modified definition of cCR at 6 months post-start of treatment to include superficial mucosal ulcerations (i.e. an 'uncertain cCR'):

1. No evidence of either mucosal tumour or submucosal swelling on white light endoscopy. A flat white scar *or superficial mucosal ulceration* remains, with or without telangiectasia
2. No palpable tumour upon digital rectal examination
3. High resolution pelvic MRI scanning shows either a linear scar only, or dense fibrosis with no obvious tumour signal (mrTRG 1 or 2).

14.4 Secondary endpoint analysis

14.4.1 Acute toxicity

The proportion of participants experiencing each CTCAE grade of acute toxicities will be summarised for each treatment arm, for the overall treatment period and up to 2 weeks post the end of treatment. The number and proportion of participants experiencing grade 3 and above acute toxicities will be reported along with 95% CIs overall and by treatment arm. Differences between the arms will be assessed using a chi-squared test.

14.4.2 Compliance with treatment

Summary statistics will be presented for the total dose of radiotherapy received in each treatment arm and the duration of treatment. The proportion of participants adhering to the radiotherapy schedule will be reported and compared between the treatment arms (where applicable) using a chi-squared test. Reasons for interruption to radiotherapy schedule will be summarised. The proportion of patients receiving chemotherapy as planned, and those who experienced dose modifications will be reported including summary statistics for the level of dose reduction along with reasons where available. The effect of radiotherapy dose on chemotherapy compliance will be explored.

14.4.3 Late toxicity

The proportion of participants experiencing each CTCAE grade of late toxicities will be summarised for each treatment arm. The number and proportion of participants experiencing grade 3 and above late toxicities will be reported along with 95% CIs and compared using a chi-squared test. Summaries will be presented for the overall follow-up period.

14.4.4 PROMs

Mean scores with corresponding 95% CIs will be calculated for all domains of the EORTC QLQ-C30 and EORTC QLQ-CR29, the additional EORTC item bank questions and for the overall LARS questionnaire. Change in mean score from baseline with 95% CIs will also be reported. Summaries will be presented for each treatment group and overall, at each follow-up time point. Treatment groups will be compared using a mixed effects linear regression model, adjusted for the minimisation factors, relevant clinical characteristics and baseline QoL scores. In order to evaluate the clinical significance of any observed differences between the treatment arms, the proportions of participants showing a minimally clinically important improvement/deterioration will be calculated, as per the published guidelines.

14.4.5 Stoma rate

The proportion of participants with a stoma by 24 months post-randomisation will be reported along with 95% confidence intervals. Time from randomisation to fashioning of a stoma will be presented using Kaplan-Meier (KM) curves. The median time-to-event estimates and 95% CIs will be presented along with the log-rank test statistic (and associated p-value). Cox's Proportional Hazards (PH) model will be used to compare the time to fashioning of a stoma between the treatment arms at 24 months post-randomisation, adjusting for the minimisation factors. The hazard ratio (HR) for the experimental arm versus the control arm (where a HR < 1 would indicate the experimental arm is better than the control) will be presented along with 95% CIs and associated p-value testing for the difference between the arms. This will be the analysis of primacy.

Participants who have died time of analysis, or who have withdrawn from follow-up data collection will be censored at the last date they were known to be alive/date of withdrawal.

The assumptions of the Cox PH model will be tested.

Depending on the proportion of participant deaths, competing risk analysis and cumulative incidence function may be considered as an alternative analysis choice. Details of which will be documented in the SAP.

14.4.6 Overall survival (OS)

The proportion of participants who have died at 24 months post-randomisation will be reported along with 95% confidence intervals. OS will be presented using Kaplan-Meier (KM) curves. The median OS estimates and 95% CIs will be presented along with the log-rank test statistic (and associated p-value) which tests for a difference in the median OS. Overall survival at 24 months post randomisation will be compared between the treatment arms using Cox's Proportional Hazards (PH) model, adjusting for the minimisation factors. The hazard ratio (HR) for the experimental arm versus the control arm (where a HR < 1 would indicate the experimental arm is better than the control) will be presented along with 95% confidence intervals (CIs) and associated p-value testing for the difference between the arms. This will be the analysis of primacy.

Participants who are still alive at the time of analysis, or who have withdrawn from follow-up data collection will be censored at the last date they were known to be alive/date of withdrawal.

The assumptions of the Cox PH model will be tested.

15 Trial monitoring

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. 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.

CTRU will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

15.1 The Trial Steering Committee and the Data Monitoring and Research Ethics Committee

The trial will be overseen by an independent Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC).

The DMEC will monitor the trial data, safety including SARs, RUSAEs, treatment related mortalities and the associated ethics of the trial. Listings of SARs and RUSAEs will be provided to the DMEC on a regular basis, frequency to be determined at the first DMEC meeting. The DMEC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan, by the CTRU, at approximately 12-monthly intervals.

After each review, the DMEC will make their recommendations to the TSC about the continuation of the trial.

15.2 Data Monitoring

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment.

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However, missing data items will not be chased from participants. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

15.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of

routine management will be brought to the attention of the TSC, Sponsor and, where applicable, to individual NHS Trusts.

16 Quality Assurance Processes

16.1 Quality assurance

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF) and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006, and through adherence to CTRU Standard Operating Procedures (SOPs).

16.2 Serious breaches

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is a breach which is likely to effect to a significant degree:

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

(b) The scientific value of the trial.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Coordinator at the CTRU.

17 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

18 Ethical approval

The trial will be submitted to and approved by a REC and the appropriate Site Specific Assessor for each participating centre prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

19 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- Consent form from participants to take part in the trial.

- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.

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

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

- Copies of participant consent forms, which will include participant names, will be sent to the CTRU when a participant is randomised into the trial. All other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.

- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.

- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

- Anonymised data for patients who also complete the discrete choice experiment survey will be shared with health economics researchers and combined with their survey responses. Explicit permission for this will be obtained from patients.

If a participant withdraws consent from further trial treatment and / or further collection of data their data will remain on file and will be included in the final trial analysis.

20 Archiving

20.1 Trial data and documents held by CTRU

At the end of the trial, data and the Trial Master File will be securely archived by CTRU in line with the Sponsor's procedures for a minimum of 15 years.

20.2 Trial data and documents held by research sites

Site data and documents will be archived at the participating research sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

20.3 Participant medical records held by research sites

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

21 Statement of indemnity

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

22 Trial Organisational Structure

22.1 Responsibilities

22.1.1 Individuals and individual organisations

Chief Investigators (CI) – The joint CIs on this study are involved in the design, conduct, co-ordination and management of the trial and will have overall responsibility for the design and set-up of the trial. However, the Clinical Oncologist CI will have primary responsibility for all clinical decisions and pharmacovigilance oversight.

Trial Sponsor (University of Leeds) – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with the NHS Research Governance Framework (RGF) and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the RGF including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any other site-specific approvals and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

22.1.2 Oversight and trial monitoring groups

Trial Management Group (TMG) – The TMG, comprising the CI, CTRU team and other key external members of staff involved in the trial, will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the REC and supporting applications for Site Specific Assessments, (iv) completing cost estimates and project initiation, (v) nominating members and facilitating the TSC and DMEC, (vi) reporting of serious adverse events, (vii) monitoring of screening, recruitment, treatment and follow-up procedures, (viii) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC) – The TSC, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two

other independent members and a PPI representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Sponsor will be invited to TSC meetings. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) – The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment and the follow-up period. The Committee will meet annually as a minimum.

23 Publication policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigators, trial leads and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the DMEC and TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

An electronic copy of peer-reviewed, published papers arising from this research will be deposited in the Europe PubMed Central database.

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25 Appendices

Appendix A - ECOG Performance Status

Table A1 ECOG Performance Status

Grade	EGOG
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
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more the 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more that 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

Appendix B - Union for International Cancer Control (UICC),TNM Classification of MALIGNANT TUMOURS, Eighth Edition

Colon and Rectum (ICD-O-3 C18-20)

Rules for Classification

The classification applies only to carcinomas. There should be histological confirmation of the disease.

The following are procedures for assessing the T, N and M categories.

Table B1 Colon and Retum Classification

T categories	Physical examination, imaging, endoscopy and/or surgical exploration
N categories	Physical examination, imaging and/or surgical exploration
M categories	Physical examination, imaging and/or surgical exploration

Table B2 Anatomical Sites and Subsites Colon and Rectum

Rectum (C20)	
Regional Lymph Nodes For each anatomical site or subsite the following are regional lymph nodes:	
Rectum	Superior, middle and inferior rectal (haemorrhoidal), inferior mesenteric, internal iliac, mesorectal (paraproctal), lateral sacra, presacral, sacral promontary (Gerota)
Metastasis in nodes other than those listed here is classified as distant metastasis.	

Table B3 Clinical Classification of Primary Tumour

TNM Clinical Classification	
TX	Primary Tumour
TX	Primary tumour invades submucosa
T0	No evidence of primary tumour
Tis[a]	Tis - Carcinoma in situ: invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3*	Tumour invades subserosa or into non-peritonealised pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures[b.c.d] and/or perforates visceral peritoneum
T4a	Tumour perforates visceral peritoneum
T4b	T4b Tumour directly invades other organs or structures

Notes

[a]Tis includes carrier cells confined within the mucosal lamia propria (intramucosal) with no extension through the muscularis mucosae into the submucosa. Tis is not used in standard UK practice.

[b]Invades through to visceral peritoneum to involve the surface.

[c]Direct invasion in T4b includes the invasion of other organs or segments of the colorectum by way of the serosa, as confirmed on microscopic examination, or for tumours in a retroperitoneal or subperitoneal locations, direct invasion of other organs or structures by virture of extension beyond the muscularis propria.

[d]Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1-3, depending on the anatomical depth of wall invasion.

*For APHRODITE trial purposes outside of UICC TNM classification, T3 will be split into: T3a: <1 mm of tumour spread beyond muscularis propria, T3b: 1-5 mm of tumour spread beyond muscularis propria), T3c: >5-15 mm of tumour spread beyond muscularis propria; T3d: >15mm of tumour spread beyond muscularis propria.

Table B4 Regional Lymph Nodes

N	Regional Lymph Nodes
NX	Regional Lymph nodes cannot be asssessed
N0	No regional lymph node metastasis
N1 N1a N1b N1c	Metastasis in 1 to 3 regional lymph nodes Metastasis in 1 regional lymph node Metastasis in 2 to 3 regional lymph nodes Tumour deposit(s), i.e. satellites,* in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastasis
N2 N2a N2b	Metastasis in 4 or more regional lymph nodes Metastasis in 4-6 regional lymph nodes N2b Metastasis in 7 or more regional lymph nodes

Note

* Tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. If a vessel wall is identifiable on H&E, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The presence of tumour deposits does not change the primary tumour T category, but changes the node status (N) to pN1c if all regional lymph nodes are negative on pathological examination.

Table B5 Distant Metastasis

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node (s)) without peritoneal metastases
M1b	Metastasis in more than one organ
M1c	Metastasis to the peritoneum with or without other organ involvement

Appendix C – Dose modifications

The guidance in this appendix should be followed wherever possible; deviation is permitted, but should be in line with local practice.

As a general principle, one dose reduction is permitted if the patient starts treatment at 100% (i.e. capecitabine at 825mg/m^2 bid or 5FU at 350mg/m^2/day plus LV). For patients where there are concerns about frailty and their overall ability to withstand chemotherapy toxicity, the treating oncologist has the discretion to lower the starting dose of capecitabine or 5FU/LV to 75% i.e. capecitabine at 620mg/m^2 b.i.d or 5FU at 260mg/m^2/d (keeping LV dose unchanged).

Supportive therapy for all toxicities should be in line with local practice.

Dose modifications for specific chemotherapy toxicities

All doses in the table below are expressed as absolute percentages of the full dose (100%)

Table C1 Dose modification for impaired renal function (only relevant to those patients receiving concurrent capecitabine)

Impaired Renal Function		
GFR - Calculated as per Cockcroft and Gault calculation (Appendix D)	Capecitabine 100% starting dose	Capecitabine 75% starting dose
<30 mL/min	Stop permanently	Stop permanently

Table C2 Dose modification for impaired liver function

Impaired Liver Function			
CTCAE Grade	**Description**	**Capecitabine or 5FU 100% starting dose**	**Capecitabine or 5FU 75% starting dose**
2	Elevated bilirubin >1.5 – 3.0 x ULN	75% dose	50% dose (i.e. 67% of 75% starting dose)
3	Elevated bilirubin >3.0 – 10 x ULN	Stop permanently	Stop permanently
≥2	ALT or AST > 3 x ULN	Interrupt until Grade 1 then restart at 75% dose	Interrupt until Grade 1 then restart at 50% dose (i.e. 67% of 75% starting dose)

Table C3 Dose modification for palmar plantar erythema

Palmar Plantar Erythema							
CTCAE Grade	Description	Capecitabine or 5 FU					
		1st appearance 100% starting dose	1st appearance 75% starting dose	2nd appearance 100% starting dose	2nd appearance 75% starting dose	3rd appearance 100% starting dose	3rd appearance 75% starting dose
1	**Clinical domain:** Numbness, dysaesthesia/parasthesia, tingling, painless, swelling or erythema. **Functional domain:** Discomfort which does not disrupt normal activities.	Full dose (100%)	75% dose	Full dose (100%)	75% dose	Full dose (100%)	75% dose
2	**Clinical domain:** Painful erythema, with swelling. **Functional domain:** Discomfort which affects activities of daily living.	Interrupt treatment until resolved to Grade 0-1, then continue at full dose (100%)	Interrupt treatment until resolved to Grade 0-1, then continue at full dose (75%)	Interrupt treatment until resolved to Grade 0-1, then continue at 75% dose	Interrupt treatment until resolved to Grade 0-1, then continue at 50% dose (i.e. 67% of 75% starting dose)	Stop permanently	Stop permanently
3	CLINICAL DOMAIN Moist desquamation, ulceration,	Interrupt treatment until resolved to Grade 0-1, then	Stop permanently	Stop permanently	NA	NA	NA

	blistering, severe pain. FUNCTIONAL DOMAIN Severe discomfort, unable to work or perform activities of daily living.	restart at 50% dose					

Supportive therapy can be used according to local policy

Table C4 Dose modification for oral mucositis

Oral Mucositis					
CTCAE Grade	Description	Capecitabine or 5 FU			
		1st appearance 100% starting dose	1st appearance 75% starting dose	2nd appearance 100% starting dose	2nd appearance 75% starting dose
1	Asymptomatic or mild symptoms; intervention not indicated	Full dose (100%)	75% dose	Full dose (100%)	75% dose
2	Moderate pain; not interfering with oral intake; modified diet indicated	Interrupt until Grade 0 – 1, then resume at 75% dose	Interrupt until Grade 0 – 1, then resume at 50% dose (i.e. 67% of 75% starting dose)	Stop permanently	Stop permanently
3	Severe pain; interfering with oral intake	Interrupt until Grade 0 – 1, then resume at 50% dose	Stop permanently	Stop permanently	NA
4	Life-threatening consequences; urgent intervention indicated	Stop permanently	Stop permanently	NA	NA

Management of chest pain whilst receiving capecitabine or 5FU

- Fluoropyrimidines are known to rarely cause a syndrome of angina like chest pain, which is thought to relate to coronary artery spasm.

- If patients develop angina like pain whilst receiving capecitabine or 5FU, then treatment should be discontinued immediately pending further assessment.
- An ECG must be performed and serum cardiac enzymes (including troponin) measured.
- Patients should be admitted overnight if significant pain has occurred within the previous 24 hours (with repeat ECGs and serum cardiac enzymes).
- If abnormalities are found on ECG or serum cardiac enzyme levels, then a cardiology opinion should be considered.
- If chest pain is deemed to be capecitabine or 5FU related, patients should not recommence this treatment. If the patient is fit to continue treatment once the episode resolves and the treating consultant agrees it is appropriate to do so, please discuss with the Trial Management Group to consider whether raltitrexed should be used as an alternative to the fluropyrimidine

Table C5 Dose modification for diarrhoea

Diarrhoea				
CTCAE Grade	Description	Capecitabine or 5FU Starting dose 100%	Capecitabine or 5FU Starting dose 75%	Radiotherapy
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Full dose (100%)	75% dose	Continue
2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; Moderate cramping	Continue as long as patient considered fit for treatment. Needs monitoring with daily patient contact by clinic visit or phone	Continue as long as patient considered fit for treatment.	Continue Manage as clinically indicated (eg. Loperamide, ensure oral hydration maintained)
3	Increase of > 7 stools per day over baseline; severe increase in ostomy output compared to baseline; limiting self-care ADL; Severe cramping or peritonism (localised guarding on abdominal examination)	Interrupt until Grade 0 – 1, ≤6mg loperamide per 24 hours required, and patient considered fit on review, then recommence at 75% dose.	Interrupt until Grade 0 – 1, ≤6mg loperamide per 24 hours required, and patient considered fit on review, then recommence at 50% dose (i.e. 67% of 75% starting dose).	For incontinence - continue. Management as per clinically indicated (eg. loperamide, codeine, iv hydration, monitor renal function), consider inpatient management for treatment and support. Check that stoma is avoided from radiotherapy portals. Do not treat if localised peritonism
4	Life threatening consequences; urgent intervention indicated	Stop permanently.	Stop permanently.	Interrupt until resolved to Grade 2. Reassess daily

Table C6 Dose modification for vomiting

Vomiting				
CTCAE Grade	Description	Capecitabine or 5FU 100% starting dose	Capecitabine or 5FU 75% starting dose	Radiotherapy
3	≥ 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalisation indicated	Interrupt until resolved to Grade 0 or 1, then restart with additional antiemetic and at 75% dose	Interrupt until resolved to Grade 0 or 1, then restart with additional antiemetic and at 50% dose (i.e. 67% of 75% starting dose)	Continue if haemodynamically stable. Manage as per clinically indicated (e.g. s/c antiemetics, IV hydration, consider TPN). Rule out alternative causes of vomiting (obstruction, ischaemic bowel etc.).
4	Life-threatening consequences; urgent intervention indicated	Discontinue permanently	Discontinue permanently	Interrupt until resolved to Grade 0 - 2. Manage as per clinically indicated (e.g. s/c antiemetics, iv hydration, consider TPN). Rule out alternative causes of vomiting (obstruction, ischaemic bowel etc.).

Table C7 Dose modification for haematological toxicity

Haematological				
CTCAE Grade	Description	Capecitabine or 5FU 100% starting dose	Capecitabine or 5FU 75% starting dose	Radiotherapy
1	Haemoglobin ≥10.0g/dL – LLN	Full dose (100%)	75% dose	Continue
	Neutrophils ≥1.5 x 10^9/L – LLN	Full dose (100%)	75% dose	Continue
	Platelets ≥75 x 10^9/L - LLN	Full dose (100%)	75% dose	Continue
2	Haemoglobin <10.0 - 8.0g/dL	Full dose (100%)	75% dose	Continue
	Neutrophils <1.5 – 1.0 x 10^9/L	Full dose (100%)	75% dose	Continue
	Platelets <75 – 50 x 10^9/L	Interrupt until resolved to Grade 0 or 1 then continue at full dose (100%)	Interrupt until resolved to Grade 0 or 1 then continue at 75% dose	Continue
3*	Haemoglobin <8.0g/dL transfusion indicated.	Interrupt until resolved to Grade 0 or 1 then restart at 75% of starting dose	Interrupt until resolved to Grade 0 or 1 then restart at 50% dose (i.e. e 67% of 75% starting dose	Continue. Transfuse in the next 24-48 hours.
	Neutrophils <1.0 – 0.5 x 10^9/L.	Interrupt until resolved to Grade 0 or 1 then restart at 75% dose	Interrupt until resolved to Grade 0 or 1 then restart at 50% dose (i.e. 67% of 75% starting dose)	Continue. Prophylactic Antibiotics (e.g. Ciprofloxacin 500mg BD)
	Platelets <50 – 25 x 10^9/L	Interrupt until Grade 0 or 1, then resume at 75% dose	Interrupt until Grade 0 or 1, then resume at 5o% dose (i.e. 67% of 75% starting dose	Continue. Consider platelet transfusion if clinically indicated (e.g. bleeding).
If patient is neutropenic and has sepsis		Stop permanently	Stop permanently	Continue, provided patient

				haemodynamically stable and considered fit for treatment.
4*	Haemoglobin - Life threatening consequences; urgent intervention indicated	Discuss with the TMG	Discuss with the TMG	Interrupt until Grade 2. Emergency transfusion, consider other causes of falling Hb (e.g. bleeding).
	Neutrophils < 0.5 x 10^9/L	Stop permanently	Stop permanently	Continue. Prophylactic Antibiotics (e.g. Ciprofloxacin 500mg BD)
	Platelets < 25 x 10^9/L	Stop permanently	Stop permanently	Interrupt until Grade 2. Consider platelet transfusion. Consider other causes of thrombocytopenia.

*Frequent blood tests must be performed in the presence of grade 3 or 4 haematological toxicity. This will range from a minimum of twice per week to daily depending on clinical circumstances

Table C8 Dose modification for radiation dermatitis

Radiation Dermatitis				
CTCAE Grade	Description	Capecitabine or 5FU 100% starting dose	Capecitabine or 5FU 75% starting dose	Radiotherapy
1	Follicular, faint or dull erythema/epilation/dry desquamation/ decreased sweating.	Full dose (100%)	75% dose	Continue
2	Tender or bright erythema, patchy moist desquamation/moderate oedema.	Full dose (100%)	75% dose	Continue. Manage skin toxicity as clinically indicated (e.g. aqueous cream or hydrocortisone on intact skin, hydrogel and non-adhesive / silicone based dressings as appropriate on areas of desquamation).
3	Confluent, moist desquamation other than skin folds, pitting oedema.	Full dose (100%)	75% dose	Continue. Manage skin toxicity as per local protocol (e.g. aqueous cream on intact skin, hydrogel and non-adhesive / silicone based dressings as appropriate on areas of desquamation). Manage pain with paracetamol, weak analgesics using WHO pain control ladder.
4	Ulceration, haemorrhage, necrosis.	Stop permanently	Stop permanently	Interrupt until Grade 3.

Table C9 Dose modification for other non-haematological toxicity

Other Non-Haematological Toxicity		
CTCAE Grade	1st appearance	2nd appearance
1	- Continue starting dose of chemotherapy (whether 100% or 75%) with supportive treatment - Continue radiotherapy	- Continue starting dose of chemotherapy (whether 100% or 75%) with supportive treatment Continue radiotherapy
2	- Interrupt chemotherapy treatment until resolved to Grade 0-1, then continue at starting dose of chemotherapy (whether 100% or 75%) with prophylaxis where possible - Continue radiotherapy	- Interrupt chemotherapy treatment until resolved to Grade 0-1, then restart at 75% if starting dose was 100% or at 50% if starting dose was 75% - Continue radiotherapy
3	- Interrupt chemotherapy treatment until resolved to Grade 0-1, then consider restart at 75% if starting dose was 100%, or at 50% if starting dose was 75%, if deemed suitable by treating clinician - Please contact trial team for advice on radiotherapy interruptions if ≥G3 toxicity excluding PPE, diarrhoea, mucositis and deranged liver function tests, haematological, radiation dermatitis or vomiting.	- Discontinue chemotherapy permanently
4	- Discontinue chemotherapy permanently - Please contact trial team for advice on radiotherapy interruptions if ≥G3 toxicity excluding PPE, diarrhoea, mucositis and deranged liver function tests, haematological, radiation dermatitis or vomiting.	

Appendix D - Cockroft & Gault formula

Males

$$\frac{\text{GFR} = 1.2 \times [140 - \text{age}] \times \text{wt (kg)}}{\text{serum creatinine (µmol/l)}}$$

Females

$$\frac{\text{GFR} = 1.2 \times [140 - \text{age}] \times \text{wt (kg)} \times 0.85}{\text{serum creatinine (µmol/l)}}$$

Appendix E – National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

Toxicities will be assessed based on the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

A copy of NCI-CTCAE is provided in the Investigator Site File.

APPENDIX F- Patient preference discrete choice experiment (DCE) study

Patients eligible for APHRODITE might be asked to participate in a patient-preference study running alongside the main trial. The DCE study is recruiting patients with rectal cancer who have not had TME surgery and who are recommended to undergo pelvic CRT as primary treatment for rectal cancer. They will be identified after discussion at the relevant MDT. Patients potentially entering APHRODITE thus represent a subgroup of all patients potentially entering the DCE study.

DCE patients will be aware that they have been recommended to undergo pelvic CRT. They may also be aware of the APHRODITE trial, but may not yet have been given trial-specific information sheets, nor been consented for entry into APHRODITE. If patients choose to participate in the DCE study, they will be asked to complete further questionnaires in addition to of the main trial questionnaires, prior to trial enrolment and during follow-up.

The DCE study will have study protocol and ethics approval separate from the main trial.

APHRODITE trial patient pathway for DCE study: Patients with early rectal cancer not suitable for radical TME surgical resection

Staging investigations complete: Biopsy confirmed adenocarcinoma of the rectum T1-T3b, N0 or Nx, M0. MDT deems patient unsuitable for radical TME resection of their tumour. Because of increased surgical risk or anticipated difficulty managing a stoma post-operatively.

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Patient seen in clinic by clinical oncologist with results and MDT decision. Treatment using chemoradiation recommended. Aims of treatment (partial/complete response) and potential acute and late toxicity discussed with patient and standard information sheets given. APHRODITE discussed and PIS given. DCE discussed and PIS given.

↓

Having had sufficient time to consider DCE and APHRODITE (typically up to a week), patient returns to clinic. DCE initially discussed and if willing, DCE consent taken by doctor or research nurse and patient then completes DCE questionnaire alone, in a quiet place outside the clinic room.

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APHRODITE then discussed back in clinic room and if willing, APHRODITE consent taken and then APHRODITE randomisation process carried out.