TRIAL PROTOCOL

STAR-TREC

V4.0

10th October 2019

Can we **S**ave the rectum by watchful waiting or **T**rans**A**nal surgery following (chemo)**R**adiotherapy versus **T**otal mesorectal excision for early **RE**ctal **C**ancer?

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Protocol development and sign off

Protocol Contributors

The Trial Management Group of the **STAR-TREC** study wrote the protocol.

CI Signature Page

Trial Name:	**STAR-TREC**
Protocol Version Number:	Version: 4.0
Protocol Version Date:	10th October 2019

This protocol has been approved by:

Name:	Mr Simon Bach
Trial Role:	Chief Investigator
Signature and date:	_____ __/__/____

Sponsor statement:

Where the University of Birmingham takes on the Sponsor role for protocol development oversight, the signing of the IRAS form by the Sponsor will serve as confirmation of approval of this protocol.

This protocol describes the **STAR-TREC** trial and provides information about procedures for patients taking part in the **STAR-TREC** trial. The protocol should not be used as a guide for treatment of patients not taking part in the **STAR-TREC** trial.

Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA5	10-Oct-2019	4.0	Substantial	Change of Clinical Trials Unit managing the study Update to membership of TMG, DMC and TSC committees Update to Background and Rationale section Implementation of the Phase III design, including an update to study aims, objectives, outcome measures and statistical considerations Update to the eligibility criteria Update to the trial entry procedure Update to the schedule of events Update to radiotherapy planning and treatment sections Modification of guidelines for capecitabine administration Inclusion of dose banding for reduced capecitabine doses Clarification of dose modifications Deletion of central review of clinical response data Modification of translational sample collection guidelines Update to HRQoL substudy guidelines Clarification of adverse event reporting procedures Minor changes to ensure clarity and consistency

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Trial Summary

TITLE	Can we **S**ave the rectum by watchful waiting or **T**rans**A**nal microsurgery following (chemo)**R**adiotherapy versus **T**otal mesorectal excision for early **Re**ctal **C**ancer? – **STAR-TREC** study
INVESTIGATOR / TRIAL LOCATION	Multicentre international study coordinated from Birmingham UK with national hubs in Radboud UMC (Netherlands) and Svendborg (Denmark).
STUDY DESIGN	International, multi-centre, open-label, rolling phase II/III trial with a partially randomised patient preference design. Patients will choose organ preservation or standard surgery. Those who prefer organ preservation will be randomised 1:1 between (i) organ preservation with mesorectal Chemoradiotherapy (CRT) versus (ii) organ preservation with mesorectal Short Course Radiotherapy (SCRT). Those who prefer standard surgery or have no preference will undergo standard Total Mesorectal Excision (TME) surgery without neoadjuvant radiotherapy treatment.
STUDY POPULATION	Subjects referred to either a colorectal surgeon or the colorectal cancer multidisciplinary team (MDT) with suspected early stage colorectal cancer identified (i) through the bowel screening programme, (ii) development of new bowel symptoms, or (iii) as part of a personal bowel surveillance programme.
ELIGIBILITY CRITERIA Note that the complete list is available in section 4, and should be referred to for eligibility assessments.	Main inclusion criteria • Biopsy proven adenocarcinoma of the rectum • Magnetic Resonance Imaging (MRI)- or Endorectal Ultrasound (ERUS)-staged TX/T1-3b, NX/N0, MX/M0 rectal tumour • MDT determines that the following treatment options are all reasonable and feasible: (a) TME surgery, (b) CRT, (c) SCRT and (d) Transanal Endoscopic Microsurgery (TEM) • Eastern Cooperative Oncology Group (ECOG) performance status 0-1 • Willing and able to consent
	Main exclusion criteria • Concomitant or previous malignancies within 3 years prior to trial entry, except those that in the opinion of the MDT are unlikely to relapse within 3 years or lead to death within 5 years • MRI node positive (≥N1, defined by protocol guidelines) • MRI extramural vascular invasion (mriEMVI) present (defined by protocol guidelines) • MRI defined mucinous tumour • Mesorectal fascia threatened by tumour (≤ 1mm on MRI or ERUS) • Maximum tumour diameter >40mm (either measured from everted edges on sagittal MRI or ERUS examination)

	• Anterior tumour location above the peritoneal reflection on MRI or ERUS • No residual luminal tumour following endoscopic mucosal resection • Prior pelvic radiotherapy • Definite evidence of regional or distant metastases (M1) in opinion of MDT • Uncontrolled cardiorespiratory comorbidity (inadequately controlled angina or myocardial infarction or arrhythmia within 6 months prior to trial entry) • Known Dihydropyrimidine Dehydrogenase deficiency • Known Gilbert's disease • Taking coumarin-derivative oral anticoagulants that cannot be stopped or substituted by low molecular weight heparin • Taking metronidazole, phenytoin, sorivudine or its analogues, such as brivudine • Women who are pregnant or lactating Age <16 years (UK), <18 years (other countries)
STUDY OBJECTIVE(S)	**STAR-TREC** is a rolling phase II/III study. The **phase II** component will assess the feasibility of a large, multi-centre randomised trial comparing radical surgery versus organ saving treatment using (chemo)radiotherapy followed by selective transanal microsurgery. The **phase III** component will evaluate two contrasting organ preservation strategies (either long-course chemoradiotherapy or short-course radiotherapy) for the treatment of early stage rectal cancer in terms of organ preservation rates, toxicity (clinician and patient-reported) and Health-Related Quality of Life (HRQoL). The phase III study will also include a standard TME radical surgery (non-randomised) comparator arm encompassing reconstructive (low anterior resection) and non-reconstructive (abdominoperineal excision, low Hartmann's procedure) approaches.
OUTCOME MEASURES FOR PHASE III	**Primary outcome:** The proportion of patients with **successful** organ preservation at 30 months from the start date of (chemo)radiotherapy. Organ preservation is considered to have **failed** (a) if the rectum is removed; (b) if the patient develops unequivocal locoregional cancer recurrence or (c) if the patient has a stoma. **Secondary outcomes:** **A) Secondary outcomes for the randomised comparison between organ-preserving strategies:**

	• Clinician-reported acute treatment-related toxicity up to 30 days following completion of (chemo)radiotherapy • Proportion of patients with complete response to (chemo)radiation therapy • Proportion of patients undergoing transanal local excision • Time to event of organ loss assessed for patients who prefer organ preservation; defined as the length of time from the start date of trial treatment until TME surgery • Non-regrowth pelvic tumour control to 36 months; defined as the length of time from the start date of trial treatment until death (any cause) or development of unequivocal pelvic recurrence **but not including** patients who developed local regrowth which was resected with clear margins using standard TME surgery • Metastasis-free survival to 36 months; defined as the length of time from the start date of trial treatment until death (any cause) or detection of distant metastasis • Non-regrowth -disease free survival to 36 months; defined as the length of time from the start of trial treatment until death (any cause), detection of local pelvic recurrence or distant metastasis **but not including** patients who developed local regrowth which was resected with clear margins using standard TME surgery • Overall survival to 60 months; defined as the length of time from the start date of trial treatment until death (any cause) **B) Secondary endpoints for analyses incorporating the non-randomised standard surgery comparator:** • Clinician-reported acute treatment related toxicity up to 30 days following completion of (chemo)radiotherapy or date of initial surgery • Non-regrowth pelvic tumour control to 36 months; defined as the length of time from the start date of trial treatment or date of initial surgery until death (any cause) or development of unequivocal pelvic recurrence **but not including** patients who preferred organ preservation and developed local regrowth which was resected with clear margins using standard TME surgery • Metastasis-free survival to 36 months; defined as the length of time from the start date of trial treatment or date of initial surgery until death (any cause) or detection of distant metastasis • Disease-free survival to 36 months; defined as the length of time from the start date of trial treatment or date of initial surgery until death (any cause), detection of local pelvic recurrence or distant metastasis **but not including** patients who developed local regrowth which was resected with clear margins using standard TME surgery

	• Overall survival to 60 months; defined as the length of time from the start date of trial treatment or date of initial surgery until death (any cause) • Decision regret at 12 and 24 months **C) Secondary endpoint for analyses of patient-reported outcomes** • Symptomatic toxicity, health economics and HRQoL measured at 3, 12, 24 and 36 months compared to baseline using validated questionnaires (HRQoL booklet) This analysis will be conducted incorporating the following comparisons: a. Randomised comparison between organ-preserving strategies b. Non-randomised comparison between organ preserving strategies and the standard surgery comparator
TRIAL ENTRY AND PATIENT PATHWAY	Patients will choose organ preservation or standard surgery. Those who prefer organ preservation will randomise 1:1 between: (i) Organ preservation with mesorectal CRT (ii) Organ preservation with mesorectal SCRT Those who prefer standard surgery or have no preference, will undergo standard TME surgery without neoadjuvant radiotherapy treatment. For organ-preserving strategies, clinical response to radiotherapy determines the next treatment step. Radiotherapy response is evaluated using clinical exam, endoscopy and MRI. The **first assessment at 11-13 weeks** (from radiotherapy start) using composite clinical, endoscopic and MRI based assessment will identify a minority of non-responders who should convert to TME surgery. **Patients demonstrating a satisfactory radiotherapy response at 11-13 weeks will be reassessed by endoscopy at 16-20 weeks**. Re-evaluation at 16-20 weeks determines if the **STAR-TREC** criteria for complete response (CR) are met. Patients who achieve CR may progress directly to active surveillance. Those who do not fulfil the criteria for CR will progress to excision biopsy with TEM.
DOSE AND TREATMENT REGIMEN FOR ORGAN SAVING STRATEGIES	**A. Long course concurrent chemoradiation (CRT):** Capecitabine: 825 mg/m² orally, b.d., on radiotherapy days Radiotherapy: A dose of 50 Gy applied to the primary tumour and surrounding mesorectum in 25 fractions of 2 Gy, 5 days a week. or **B. Short course radiotherapy (SCRT):** A dose of 25 Gy applied to the primary tumour and surrounding mesorectum in 5 fractions of 5 Gy, 5 days a week.

EVALUATION OF RESPONSE TO (CHEMO) RADIOTHERAPY TREATMENT	• 1st clinical assessment of primary tumour **11-13 weeks** from start of (chemo)radiotherapy using composite clinical, endoscopic and MRI based assessment. o Poor response (see protocol) – convert to TME surgery. o Satisfactory response (see protocol) – proceed to 2nd clinical assessment at 16-20 weeks. • 2nd clinical assessment of primary tumour **16-20 weeks** from start of (chemo)radiotherapy using endoscopy. o Complete response (see protocol) – watch and wait strategy. o Does not meet criteria for complete response – transanal local excision using TEM or equivalent surgical platform. • Assessment of toxicity and postoperative complications. • Histopathological assessment of the resected rectal specimen to report (a) Presence of clear margins (>1mm from excision border to tumour edge), (b) TNM staging.
PLANNED SAMPLE SIZE	**Phase II:** Recruitment will be assessed over a two-year period (following 6 month initial setup). In year 1 we aim to recruit 4 subjects per month. In year 2 we aim to recruit a minimum of 6 patients per month. Aggregate total of 120 international cases (80 patients recruited to the organ preservation arms (CRT and SCRT) and 40 patients recruited to the standard surgery arm). If recruitment is on target in year 2, we would apply for funding and a major protocol amendment to continue the trial into phase III.The phase II component will be closed once approximately 120 patients are recruited and all necessary approvals for protocol version 4.0 implementing the phase III design are obtained. The phase II component will be closed once approximately 120 patients are recruited and all necessary approvals for protocol version 4.0 implementing the phase III design are obtained. **Phase III:** 300 patients randomised internationally to the organ preservation arms (CRT and SCRT). Estimated 80 patients recruited internationally to the standard surgery comparator arm. Recruitment period: 4 years. **Total for combined Phase II/III:** 380 patients randomised to the organ preservation arms (CRT and SCRT). Estimated 120 patients recruited to the standard surgery comparator arm.
DURATION OF STUDY PERIOD (per subject)	All patients (phase II and phase III) will be followed up for 36 months from the start date of (chemo)radiotherapy or initial surgery.

Trial Schema

Phase II:

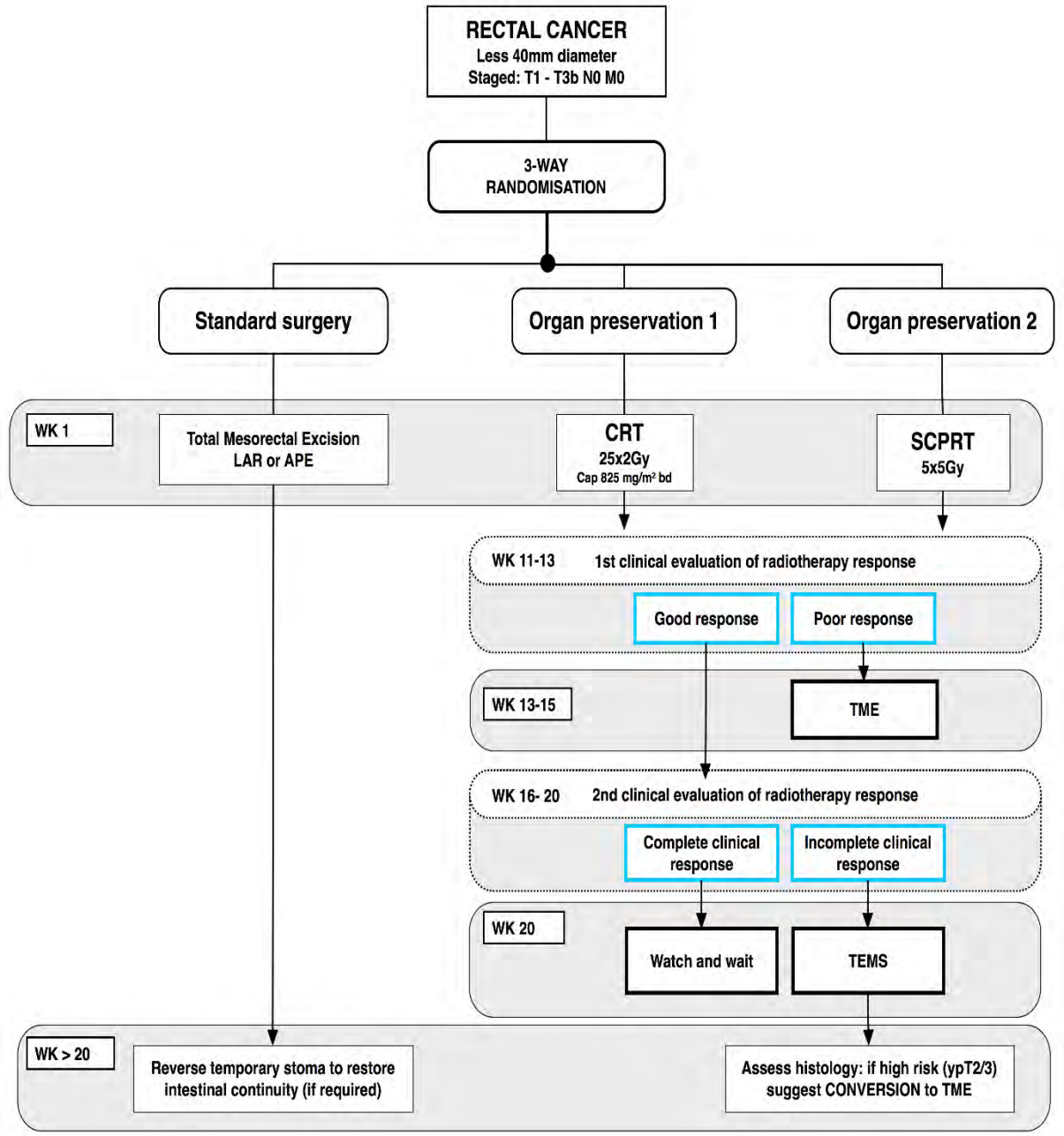

Figure 1a: STAR-TREC Phase II trial schema including a **3-way randomisation**.

Phase III:

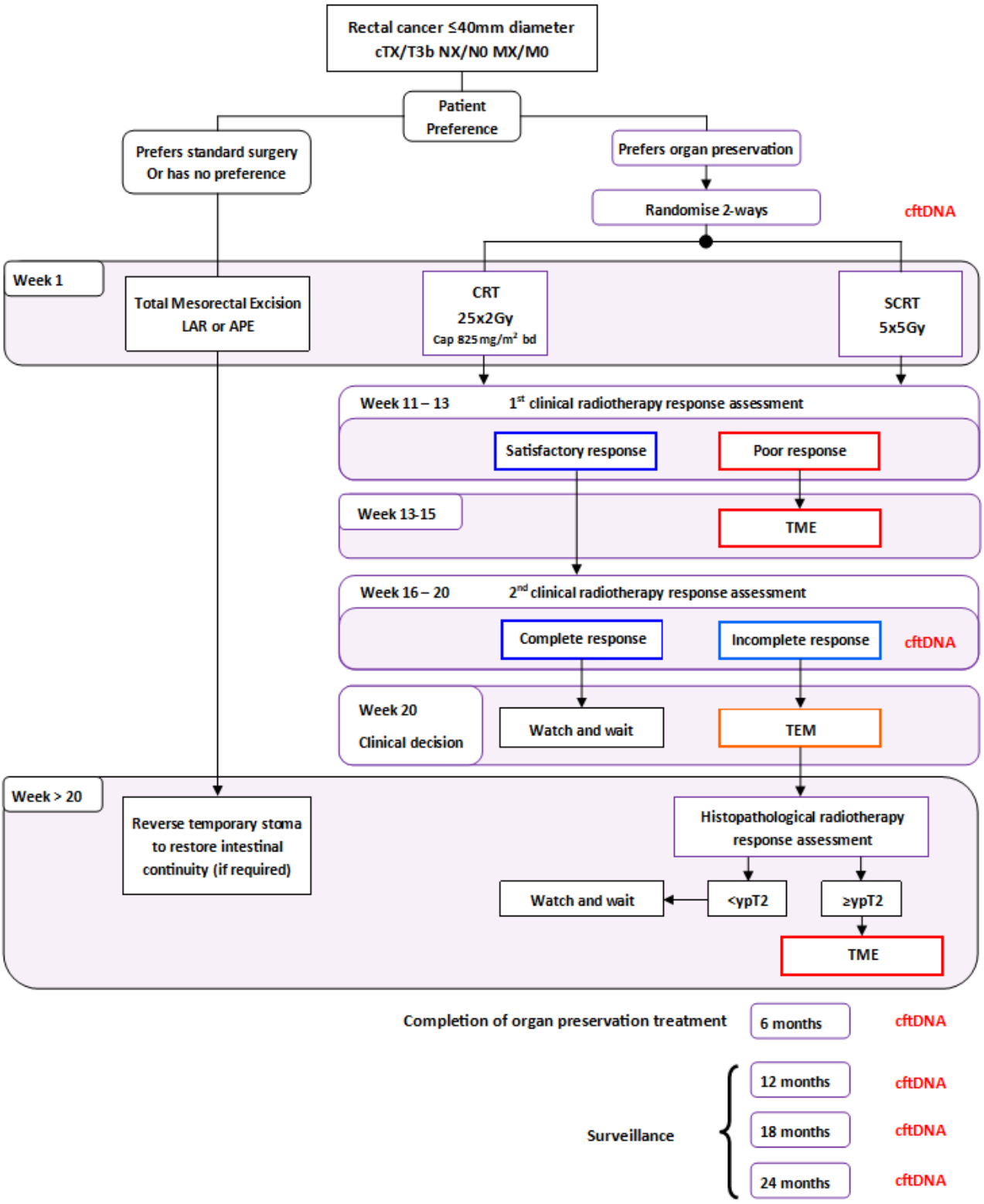

Figure 1b: STAR-TREC Phase III (revised) study schema incorporating new **partially randomised patient preference design**.

Schedule of events

Standard TME Surgery Arm

	Screening		REGISTRATION	Treatment*			Follow-up*[b]				
	Within 42 days‡	Within 7 days‡		Weeks 1-6#	Weeks 11-13	>Week 20	6 months	12 months	24 months	30 months	36 months
Written informed consent	X[a]										
Medical history[1]	X										
ECOG performance status	X										
Physical examination	X						X	X	X	X	X
Colonoscopy[2]	X							X[c]			
Histopathology[3]	X			X							
Computerized Tomography (CT) scan thorax, abdomen and pelvis with contrast[4]	X								X		X
High resolution MRI pelvis[5]	X								X[d]		X[d]
Endorectal ultrasound (ERUS)[6]	X										
MDT review	X										
Preparation and shipment of FFPE tissue blocks and matched H&E slides[7]	X			X							
Health related quality of life booklet[8]	X				X			X	X		X
Concomitant medication safety check		X									
Confirmation of eligibility		X									
Pre-surgical assessment				X							
TME surgery[9]				X							
Stoma formation				X							
Stoma reversal (if required)						X					
Adverse events review/reporting[10]				X		X					
Surgical morbidities review/reporting[11]				X		X					
Survival status				X		X	X	X	X	X	X

* Calculated from the date of TME surgery

‡ Prior to date of trial entry

\# Timeframe provided for guidance only. TME surgery and associated activities beyond 6 weeks are allowed if reason documented in the medical notes

1 Medical history to include details of current colorectal cancer, previous and current medical conditions and previous treatments received.

2 Colonoscopy with biopsy to be performed for all patients prior to trial entry. At least one colonoscopy to be performed within the first 3 years of follow-up and as per national guidelines.

3 Histopathological assessment required for baseline diagnostic biopsy and surgical resection specimens.

[4] CT-Thorax-abdomen-pelvis to be performed for all patients prior to trial entry. At baseline it is recommended within 42 days of registration but a maximum of 63 days prior to trial entry is permitted. At 24 and 36 months all patients to have either a CT-Thorax-abdomen-pelvis **OR** CT-thorax-abdomen and high resolution MRI pelvis.

[5] High resolution MRI should be performed for all patients prior to trial entry. It is recommended within 42 days of registration but a maximum of 63 days prior to trial entry is permitted.

[6] ERUS to be used at baseline where the patient is unable to tolerate MRI. Optional ERUS may also be used to supplement MRI in centres where this is available.

[7] Provided that patient has consented for tissue to be used for research purposes. Samples to be labelled with trial number and local histology number only and sent to the national histopathology laboratory.

[8] EORTC QLQ CR29 & C30, EQ-5D-5L, Low Anterior Resection Syndrome (LARS) score and The International Consultation on Incontinence Modular Questionnaire on Male Lower Urinary Tract Symptoms (ICIQ-MLUTS)/ ICIQ-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) to be completed at each of the time points after specific informed consent has been obtained.

[9] Permitted techniques include (reconstructive) low anterior resection and (non-reconstructive) abdominoperineal excision or low Hartmann's procedure.

[10] AEs / SAEs to be reported according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 within 30 days of surgery. Surgical SAEs should also be classified using the Clavien-Dindo system.

[11] Surgical morbidities will be recorded post-operatively until 30 days after each surgery.

[a] Written informed consent required prior to performing any trial-specific procedure. Assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated time frame prior to registration.

[b] Every effort should be made to schedule follow-up assessments as specified in the protocol. Annual follow-up will continue until 36 months from date of initial surgery. Further follow-up is according to national guidelines.

[c] At least one colonoscopy to be performed within the first 3 years after treatment and as per national guidelines. When colonoscopy is performed, a flexible sigmoidoscopy is **NOT** required.

[d] MRI pelvis at 24 and 36 months **only** required if CT pelvis is **not** performed at these time points.

Organ preservation with long course chemo-radiotherapy (CRT)

	Screening			Treatment*					Follow-up*[b]								
				Week													
	Within 42 days‡	Within 7 days‡		1	2	3	4	5	Week 11-13	Week 16-20	>Week 20	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Written informed consent	X[a]																	
Medical history[1]	X																	
ECOG performance status	X																	
Physical examination	X								X	X		X	X	X	X	X	X	X
Digital rectal examination	X								X	X		X	X	X	X	X	X	X
Colonoscopy[2]	X															X[c]		
Histopathology[3]	X								X	X	X							
CT scan thorax, abdomen and pelvis with contrast[4]	X															X[d]		X[d]
High resolution MRI pelvis[5]	X								X			X	X	X	X	X	X	X
Endorectal ultrasound (ERUS)[6]	X																	
MDT review	X																	
Translational blood sample collection and shipment[7]	X									X		X		X	X	X		
Preparation & shipment of FFPE tissue blocks and matched H&E slides[8]	X																	
Health related quality of life booklet[9]	X								X					X		X		X
Radiotherapy planning	X																	
Pregnancy test (urine hCG or serum βhCG)		X																
Concomitant medication safety check		X																
Confirmation of eligibility		X																
Weight and height[10]		X																
Haematology and biochemistry[11]				X	X	X	X	X										
Capecitabine 825 mg/m^2 bd on radiotherapy days				X	X	X	X	X										
Radiotherapy 25x2Gy, 5 days a week				X	X	X	X	X										
Rectal endoscopy[12]									X	X		X	X	X	X	X	X	X
Pre-surgical assessment (if required)									X	X	X							
TME surgery[13#]									X[e]		X[f]							
TEM surgery[14]										X[g]								
Surgical morbidities review/reporting[15]									X	X	X	X						
Adverse events review/reporting[16]				X	X	X	X	X	X	X	X							
Survival status				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

RANDOMISATION

* Calculated from the date that chemoradiotherapy treatment commenced

‡ Prior to date of trial entry, unless otherwise specified.

\# **If patient converted to TME surgery then follow up should be performed according to the schedule of events for the standard TME surgery arm (see 9.5.2)**

1 Medical history to include details of current colorectal cancer, previous and current medical conditions and previous treatments received.

2 Colonoscopy with biopsy to be performed for all patients prior to trial entry. At least one colonoscopy to be performed within the first 3 years of follow-up and as per national guidelines.

3 Histopathological assessment required for baseline diagnostic biopsy and surgical resection specimens if patient undergoes TME or TEM.

4 CT-Thorax-abdomen-pelvis to be performed for all patients prior to trial entry. At baseline it is recommended within 42 days of registration but a maximum of 63 days prior to trial entry is permitted. At 24 and 36 months all patients to have either a CT-Thorax-abdomen-pelvis **OR** CT-thorax-abdomen.

5 High resolution MRI should be performed for all patients prior to trial entry. It is recommended within 42 days of registration but a maximum of 63 days prior to trial entry is permitted.

6 ERUS to be used at baseline where the patient is unable to tolerate MRI. Optional ERUS may also be used to supplement MRI in centres where this is available.

7 Provided that patient has consented for tissue to be used for research purposes. 50ml peripheral blood to be collected and sent to national processing laboratory.

8 Provided that patient has consented for tissue to be used for research purposes. Samples to be labelled with trial number and local histology number only and sent to the national histopathology laboratory.

9 EORTC QLQ CR29 & C30, EQ-5D-5L, LARS score and ICIQ-MLUTS/ ICIQ-FLUTS to be completed at each of the time points after specific informed consent has been obtained.

10 Height and weight may be taken at any time after randomisation and prior to starting chemoradiotherapy. If patient experiences toxicities mandating capecitabine dose reductions, weight to be measured again prior to re-dispensing adjusted dose.

11 Haematology and biochemistry to include creatinine clearance, white blood cell count, absolute neutrophil count, platelets, Alanine Transaminase (ALT) or Aspartate Aminotransferase (AST), bilirubin.

12 Rectal endoscopy (e.g. colonoscopy, flexible sigmoidoscopy, proctoscopy) to be performed at these time-points. At least one colonoscopy to be performed within the first 3 years.

13 Includes (reconstructive) low anterior resection and (non-reconstructive) abdominoperineal excision or low Hartman's procedure.

14 Includes transanal endoscopic microsurgery or equivalent transanal surgical technique.

15 Surgical morbidities will be recorded post-operatively until 30 days after each surgery.

16 AEs / SAEs to be reported according to the CTCAE v4.03 from date that trial treatment commences until 30 days after the administration of last trial treatment. Surgical SAEs should also be classified using the Clavien-Dindo system.

a Written informed consent required prior to performing any trial-specific procedure. Assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated time frame prior to registration.

b Every effort should be made to schedule follow-up assessments as specified in the protocol. Annual follow-up will continue until 36 months from the start of chemo-radiotherapy. Further follow-up is according to national guidelines

c At least one colonoscopy to be performed within the first 3 years after treatment and as per national guidelines.

d CT-thorax-abdomen **OR** CT-thorax-abdomen-pelvis to be completed at 24 and 36 months.

e Conversion to TME surgery to be performed within 4 weeks of the 11-13 week clinical assessment for patients showing poor response to CRT as per protocol guidelines.

f Conversion to TME surgery to be completed within 8-16 weeks of initial transanal surgical procedure for patients showing high risk features on TEM specimen as per protocol guidelines.

g TEM surgery to be performed within 4 weeks of 16-20 week clinical assessment for patients with clinically satisfactory, yet incomplete tumour response at 16-20 weeks.

Organ preservation with short course radiotherapy (SCRT)

	Screening			Treatment*	Follow-up*[b]									
	Within 42 days‡	Within 7 days‡		Week 1	Week 11-13	Week 16-20	>Week 20	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Written informed consent	X[a]													
Medical history[1]	X													
ECOG performance status	X													
Physical examination	X				X	X		X	X	X	X	X	X	X
Digital rectal examination	X				X	X		X	X	X	X	X	X	X
Colonoscopy[2]	X											X[c]		
Histopathology[3]	X				X	X	X							
CT scan thorax, abdomen and pelvis with contrast[4]	X											X[d]		X[d]
High resolution MRI pelvis[5]	X				X			X	X	X	X	X	X	X
Endorectal ultrasound (ERUS)[6]	X													
MDT review	X													
Translational blood sample collection and shipment[7]	X					X		X		X	X	X		
Preparation and shipment of FFPE tissue blocks & matched H&E slides[8]	X													
Health related quality of life booklet[9]	X				X					X		X		X
Radiotherapy planning	X													
Pregnancy test (urine hCG or serum βhCG)		X												
Concomitant medication safety check		X												
Confirmation of eligibility		X												
Radiotherapy 5x5Gy – over 5 days				X										
Rectal endoscopy[10]					X	X		X	X	X	X	X	X	X
Pre-surgical assessment (if surgery required)					X	X	X							
TME surgery[12#]					X[e]		X[f]							
TEM surgery						X[g]								
Surgical morbidities review/reporting[13]					X	X	X	X						
Adverse events review/reporting[14]				X	X	X	X							
Survival status				X	X	X	X	X	X	X	X	X	X	X

RANDOMISATION

* Calculated from the date that radiotherapy treatment commenced

‡ Prior to date of trial entry

\# **If patients undergo TME surgery then follow up should be performed according to the schedule for the radical surgical arm (see 9.5.2)**

1 Medical history to include details of current colorectal cancer, previous and current medical conditions and previous treatments received.

2 Colonoscopy with biopsy to be performed for all patients prior to trial entry. At least one colonoscopy to be performed within the first 3 years of follow-up and as per national guidelines.

3 Histopathological assessment required for baseline diagnostic biopsy and surgical resection specimens if patient undergoes TME or TEM.

4 CT-Thorax-abdomen-pelvis to be performed for all patients prior to trial entry. At baseline it is recommended within 42 days of registration but a maximum of 63 days prior to trial entry is permitted. At 24 and 36 months all patients to have either a CT-Thorax-abdomen-pelvis OR CT-thorax-abdomen.

5 High resolution MRI should be performed for all patients prior to trial entry. It is recommended within 42 days of registration but a maximum of 63 days prior to trial entry is permitted.

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10 Rectal endoscopy (e.g. colonoscopy, flexible sigmoidoscopy, proctoscopy) to be performed at these time-points. At least one colonoscopy to be performed within the first 3 years.

11 Includes (reconstructive) low anterior resection and (non-reconstructive) abdominoperineal excision or low Hartman's procedure.

12 Includes transanal endoscopic microsurgery or equivalent transanal surgical technique.

13 Surgical morbidities will be recorded post-operatively until 30 days after each surgery.

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a Written informed consent required prior to performing any trial-specific procedure. Assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated time frame prior to registration.

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c At least one colonoscopy to be performed within the first 3 years after treatment and as per national guidelines.

d CT-thorax-abdomen **OR** CT-thorax-abdomen-pelvis to be completed at 24 and 36 months.

e Conversion to TME surgery to be performed within 4 weeks of the 11-13 week clinical assessment for patients showing poor response to radiotherapy as per protocol guidelines.

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g TEM surgery to be performed within 4 weeks of 16-20 week clinical assessment for patients with clinically satisfactory, yet incomplete tumour response at 16-20 weeks.

Abbreviations

ACPGBI: Association of Coloproctology of Great Britain and Ireland
ADL: Activities of Daily Living
ALT: Alanine Transaminase
AE: Adverse Event
AR: Adverse Reaction
AST: Aspartate Aminotransferase
CRP: C-Reactive Protein
CRT: Chemoradiotherapy
CR: Complete Response
CRF: Case Report Form
CRCTU: Cancer Research UK Clinical Trials Unit
CT: Computerized Tomography
CTCAE: Common Terminology Criteria for Adverse Events
ctDNA: circulating tumour Deoxyribonucleic Acid
DMC: Data Monitoring Committee
DPYD: Dihydropyrimidine Dehydrogenase
ECOG: Eastern Cooperative Oncology Group
EMVI: Extramural Vascular Invasion
EORTC: European Organization for Research and Treatment of Cancer
ERUS: Endorectal Ultrasound
eRDC: electronic Remote Data Capture
FFPE: Formalin Fixed Paraffin-embedded
GCP: Good Clinical Practice
GFR: Glomerular Filtration Rate
FDG-PET: Fluorodeoxyglucose-Positron Emission Tomography
H&E: Haematoxylin and Eosin
HRQoL: Health-Related Quality of Life
HTA: Human Tissue Authority
ICIQ- FLUTS: The International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms
ICIQ-MLUTS: The International Consultation on Incontinence Modular Questionnaire on Male Lower Urinary Tract Symptoms
IMP: Investigational Medicinal Product
LARS: Low Anterior Resection Syndrome
MDT: Multidisciplinary Team
MHRA: Medicines and Healthcare products Regulatory Agency
MRI: Magnetic Resonance Imaging
NICE: National Institute for Health and Care Excellence
SAE: Serious Adverse Event
SAR: Serious Adverse Reaction
SCRT: Short Course Radiotherapy
SUSAR: Suspected Unexpected Serious Adverse Reaction
TEM: Transanal Endoscopic Microsurgery
TME: Total Mesorectal Excision
TMG: Trial Management Group
ULN: Upper Limit of Normal

Table of Contents

1. Background and Rationale

1.1. Background

1.1.1. Increasing incidence of early rectal cancer poses new surgical dilemma

Bowel cancer is the second most common tumour with 41 000 new cases diagnosed annually in the UK, 447 000 across Europe and 1.36 million worldwide; of which one third are located in the rectum. Historically, these tumours presented symptomatically at a relatively advanced stage. Introduction of bowel screening combined with improved access to diagnostic testing has greatly increased the proportion of patients diagnosed with **early stage** rectal cancer from 8% to 25%.(1, 2) The new faecal immunochemical test (FIT) is a much more convenient screening tool and will further promote early diagnosis. Surgery to remove the rectum (no radiotherapy) is the current standard of care for treatment of early stage rectal cancer, (3) however, this approach is associated with substantial morbidity, occasional mortality and significant impairment to quality of life. Radical surgery is likely to overtreat the majority of these early tumours.

1.1.2. Current standard care for early stage rectal cancer

Standard primary radical Total Mesorectal Excision (TME) surgery is an oncologically effective treatment for early stage rectal cancer; only 2% and 12% of patients experience local or distant failure respectively.(4-6) However, resection of a low rectal tumour requires a permanent stoma in approximately 10% of cases while many more patients have a temporary stoma, some of which are not reversed. Six-month mortality following radical curative surgery for rectal cancer is 4.6% for patients aged 65-74 years rising to 13.4% for patients aged 75-84 years.(7, 8) The Dutch TME trial, reported clinical bowel leaks in 16% of non-irradiated patients.(9) Pelvic dissection may inadvertently cause autonomic nerve damage leading to urinary incontinence or retention (25%-34%) and sexual dysfunction.(10, 11) 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.(12, 13) Three prospective cohort studies have examined health related quality of life scores following rectal cancer surgery (see below).(12, 14, 15) Each demonstrated persistently poor social, role, body image and defaecation scores. There are hence concerns that radical surgery, which evolved to treat locally advanced, symptomatic tumours, may not be the

optimal method of treatment for early screen-detected tumours. An organ preserving strategy may generate significantly less morbidity without substantially compromising oncological outcomes.

1.1.3. Local excision alone for early rectal cancer

Early rectal tumours may be locally excised through the anus with low morbidity and mortality using Transanal Endoscopic Microsurgery (TEM).(16, 17) Local disc excision of the primary tumour, plus an adequate margin of normal tissue, allows for saving of the rectum. Morbidity and mortality after local excision are lower than after radical resection; in a study of 5,305 patients with early-stage rectal cancer, 30-day mortality after local excision was found to be 0.5% compared with 2.4% in patients undergoing radical resection (P = 0.008). Morbidity within 30 days of surgery was 4.4% in the local excision group versus 12.7% in the radical resection group (P < 0.001).(18)

However, several case series have reported inadequate long-term oncological results of transanal excision with local recurrence rates ranging from 5% to 28% for T1 lesions, and from 11% to 45% for T2 lesions.(6, 19) With no prospective randomised trials of local excision versus radical resection, these rates of recurrence are higher than would be expected for cancers treated with radical resection. Omission of total mesorectal excision also risks leaving behind microscopic lymph node metastases, a potential cause of local failure. The risk of lymph node involvement increases with depth of wall penetration, but there can be lymph node involvement even in patients with only T1 invasion of the rectal wall. The incidence of lymph node metastasis ranges from 6% to 14% for T1 tumours, 17% to 23% for T2 tumours, and 49% to 66% for T3 tumours.(20)

Following local excision alone, the majority of cases, perhaps 75%, have an intermediate probability of local recurrence (10-30%). Histopathological risk stratification lacks precision, and is unable to discriminate reliably between cases that have been effectively treated by local excision from those where conversion to radical TME surgery would be beneficial.(16) Conversion of all intermediate risk patients to radical surgery would provide no additional benefit for the majority, although taking no further action would result in unacceptable levels of recurrence. Selective post-operative radiotherapy for ‘high-risk’ cases has failed to deliver satisfactory improvements in disease control.(16, 21) For advanced rectal cancers, pre-operative radiotherapy is more effective than post-operative radiotherapy and its benefits

include eradication of micrometastatic/ small volume residual nodal disease in the mesorectum. (22, 23)

1.1.4. Magnetic Resonance Imaging assessment

Pelvic Magnetic Resonance Imaging (MRI) is used to determine the clinical stage of all newly diagnosed rectal cancer. Increasing clinical stage on MRI is associated with a higher risk of local recurrence following radical surgery and National Institute for Health and Care (NICE) have recommended that patients rated at moderate or high risk of local recurrence undergo pre-operative chemoradiotherapy (CRT) using a concurrent fluoropyrimidine which reduces risk of local relapse by 50%.(24) **Pre-treatment MRI characterises early stage rectal cancer as low risk of local treatment failure and consequently NICE and Association of Coloproctology of Great Britain and Ireland (ACPGBI) recommend that patients undergo radical surgery following the principles of TME without (chemo)radiotherapy.(3) Patients with early rectal cancer should only receive CRT or Short Course Radiotherapy (SCRT) as part of a clinical trial.**

1.1.5. Pelvic radiotherapy

Efficacy of preoperative radiotherapy in combination with radical surgery

A Cochrane review has demonstrated that preoperative radiotherapy reduces local recurrence in operable rectal cancer.(25) Four large randomised clinical trials, involving over 4000 rectal cancer patients from three countries, show that the addition of preoperative radiotherapy to radical TME surgery reduces the incidence of local recurrence in both early and locally advanced disease.(22, 23, 26, 27) However, there is no international consensus on the optimum radiotherapy schedule. The two most common schedules are preoperative CRT (45-50.4Gy in combination with fluoropyrimidine based chemotherapy) and short course radiotherapy (25Gy in five fractions). No significant difference in local recurrence rates has been reported between the two schedules when used preoperatively in resectable disease.(28, 29) NICE guidelines consider both treatment approaches appropriate as pre-operative treatment of patients with “moderate risk” resectable rectal cancer.

‘Long course’ CRT is the established treatment for downstaging advanced rectal tumours that encroach upon the surgical margin according to pre-operative MRI. Two trials have demonstrated the benefit of adding concurrent chemotherapy to ‘long course radiotherapy’ leading to a higher complete response rate and a lower local recurrence rate after 5 years of

follow-up.(30, 31) In a German randomised trial, 10.3% of patients had a pathological complete response (pCR) following CRT with no viable tumour identified after resection.(32) None of these patients developed local recurrence, and they had a better disease-free survival than those without a pCR. Similar findings have also been reported in several other case series.(33, 34)

Short course radiotherapy (SCRT) is mainly used to reduce the incidence of local recurrence where pre-operative MRI indicates clear surgical margins. There is substantial experience of this regimen in European countries and it is associated with less acute toxicity and similar late toxicity when compared with pre-operative CRT. The risk of local recurrence where margins appear clear depends on the quality of the TME specimen together with indicators of locoregional tumour dissemination such as N+ and EMVI. SCRT has been mainly used with a short interval to surgery and in this context is not expected to result in significant downstaging.(35) However SCRT may effectively downstage locally advanced tumours if surgery is delayed.(36, 37) Short course radiotherapy with a delay to surgery has been evaluated as a treatment arm in the Stockholm 3 trial, with low toxicity and a 12.5% pCR rate for this regimen.(38, 39)

Side effects of pelvic radiotherapy

Direct comparison of neoadjuvant CRT versus SCRT schedules by Bujko et al indicated that the incidence of acute severe radiation induced toxicity (grades 3, 4, 5) was substantially higher following CRT (18%) compared to SCRT (3%).(28) The incidence of severe late toxicity was similar between groups: long course 7% versus SCRT 10%. Commonest severe late toxicities were intestinal 5.1%, bladder 1.4%, sensory-motor disturbance 2.9% and femoral neck fracture 0.7%. No differences in overall survival, disease free survival or local recurrence were observed. The Trans-Tasman Radiation Oncology Group compared SCRT versus CRT prior to TME surgery and also found no significant difference in rates of late grade 3 and 4 bowel or any late radiation toxicity. These data support the view that SCRT is better tolerated than CRT in the short term with similar long-term effects.(29) There is a need to investigate both radiotherapy schedules as potential strategies for organ saving.

1.1.6. Organ preservation for rectal cancer

Evidence supporting organ preservation derived from conventional treatment of advanced rectal cancer

While the probability of achieving organ preservation following treatment of locally advanced rectal cancer with CRT is relatively low, there is nonetheless a well-established literature on this subject. CRT is widely administered to patients with locally advanced rectal cancer. A small proportion of cases (circa 15%) appear exquisitely sensitive to treatment with complete tumour response if the organ remains in situ. CRT must eradicate all tumour tissue in order to achieve organ preservation in patients with locally advanced rectal cancer as residual tumour cells are likely to be relatively widely disseminated around the bowel wall, lying beyond the scope of local transanal surgery. Habr-Gama's group have led development of an organ saving approach for 'locally advanced' rectal cancer. Of 265 predominantly T3 rectal cancer patients treated with CRT, 71 patients (27%) had a complete clinical response.(40, 41) These patients did not have surgery and after a mean follow up of 57 months (range 18-156 months), two patients developed local recurrence, of which one was successfully salvaged. A further three patients developed isolated distant metastases. However, these results have not been consistently replicated.(42) An international watch and wait registry incorporating Habr-Gama's data reported time to relapse following a complete response to chemoradiotherapy.(43) Cases were eligible on the basis of either clinical determined complete response or less frequently pathological complete response following local transanal excision. At diagnosis patients generally had locally advanced forms of rectal cancer; only 28% were staged ≤T2, and 35% N0. With median follow up of 3.3 years, local regrowth occurred in 213 of 880 cases, with a 2-year rate of 25.2% (95% CI 22.2–28·5%). Local regrowth was diagnosed in the first year in 136 (64%) of the 213 patients. Local regrowth was diagnosed within 2 years in 188 (88%) of 213 patients.

The work of Habr-Gama et al has led us to question whether radical surgery is the most effective curative treatment for rectal cancer. Maas et al reviewed 2323 patients treated with CRT demonstrating a clear correlation between the clinical T-stage and the pCR rate (cT1: 58%, cT2: 28%, cT3: 16% and cT4: 12%).(44) Thus the success rate of an organ preserving approach that incorporates radiotherapy treatment will be highly dependent upon tumour stage. Neoadjuvant treatment with either CRT or SCRT may be of particular benefit to patients with early tumours, following the paradigm of anal cancer. **A key research question is whether patients with early-stage rectal cancer can safely avoid radical surgery by using an**

organ saving approach that utilises (chemo)radiotherapy and selective transanal local excision?

Utilising (chemo)radiotherapy to achieve organ preservation in early rectal cancer

Pre-operative (chemo)radiotherapy may be used to shrink or 'downstage' early rectal cancer and facilitate surgical local excision with clear margins. In addition, this treatment may effectively treat microscopic mesorectal nodal metastases and reduce the likelihood of tumour implantation at the time of local surgery. Following local excision tumour downstaging may be objectively measured. Cases of poor clinical response where the histopathological features suggest that the tumour is resistant to the effects of (chemo)radiotherapy treatment can be selectively converted to radical surgery.

A small number of prospective, non-randomised phase II studies have evaluated use of CRT in the context of early stage rectal cancer for the purpose of achieving organ preservation. These studies generally supplemented CRT with routine local transanal excision to resect the area of bowel wall originally occupied by tumour in its entirety. One study employed a radiotherapy boost to ablate residual tumour cells. Each of these studies demonstrated high rates of organ preservation and infrequent pelvic cancer recurrence; but this was at the cost of significant treatment related toxicity.(45-48) An overview of prospective studies that have evaluated use of (chemo)radiation and routine local excision in early rectal cancer is provided in Table 1. These studies recorded histopathological downstaging in the locally excised surgical specimen to quantify the degree of tumour regression. Patients with a favourable response were selected for active observation, while those judged to have an inadequate or poor response were counselled to undergo conversion from an organ preserving approach to radical surgery. Overall these studies achieved organ preservation rates of 64-74%. It should be noted that two studies commenced watchful waiting for all patients following (chemo)radiotherapy and routine local excision, regardless of the histopathological response to CRT and consequently achieved higher organ preservation rates of 91-92%. Isolated local relapse occurred in 4-6% of cases but the majority were successfully salvaged. Distant metastasis rates of 10-15% within 36 months were in keeping with stage I rectal cancer. (49). Putting aside issues of toxicity that undermined many of these studies, multimodality therapy for early stage rectal cancer provided good oncological outcomes, particularly when viewed in the context of organ preservation studies that utilised TEM alone; where local recurrence rates were 18% in pT1, 29% in pT2 and 50% in pT3. (50)

The phase III GRECCAR 2 study enrolled patients with early rectal tumours following a good clinical response to CRT.(51). Patients were then randomly allocated to conventional radical surgery versus routine local transanal tumour excision. Specimens were histologically staged following local excision and those deemed to be radioresistant i.e. no downstaging (>=ypT2) were converted to radical surgery. The composite primary endpoint failed to show superiority of organ preservation over standard surgery (with CRT) largely as a consequence of the cumulative toxicity associated with multiple treatment modalities (CRT, routine local excision and TME surgery). While this is mainly due to patients who failed organ preservation, routine use of local excision 13 weeks after commencement of CRT is a contributing factor. Tumour regression may continue beyond this point and waiting longer to perform transanal excision may have reduced the proportion of cases that required conversion to standard surgery. GRECCAR II found no residual tumour, termed pathological complete response (pCR), in 40% of local excision specimens. This figure is in keeping with phase II studies that evaluated (chemo)radiation and local transanal excision for organ preservation in early rectal cancer.(45, 48, 52) **It is questionable whether routine local excision benefits patients who achieve complete response and a selective approach to transanal local excision may significantly reduce treatment related toxicity.**

Study	n	Therapy	Timing of surgery (weeks)	Organ Preservation	All recurrence (local + distant)	Isolated local recurrence	Salvage surgery
ACOSOG Z6041 [a]	79	CRT Oxaliplatin	9-13	72 (91%)	8/79 (10%)	3/79 (4%)	2/3
CARTS [b]	55	CRT	8-10	41/55 (74%)	7/55 (12%)	2/55 (3%)	2/2
TREC [b]	27	SCRT	8-10	19 (70%)	3/27 (11%)	1 (4%)	0/1*
TREC [a]	61	SCRT	8-10	56 (92%)	9/61 (14%)	4 (6%)	-
GRECCAR 2 [b]	73	CRT	13	47 (64%)	11/73 (15%)	5 (5%)	4/5 *
Total	**295**			**235 (79%)**	**38 (12%)**	**15 (5%)**	**-**

Table 1: Prospective studies evaluating organ preservation in early rectal cancer utilising (chemo)radiotherapy and routine transanal local excision followed by [a] surveillance of all patients or [b] histopathological assessment of tumour downstaging with conversion of poor responders to radical surgery.(45, 46, 48, 51) Minimum 2 year follow up. *patient technically salvageable with radical surgery but refused treatment.

TREC (ISRCTN14422743) and GRECCAR 2 were the only studies to include a standard 'radical' surgery comparator; in GRECCAR 2 these patients also received neoadjuvant CRT while in TREC the control arm was unirradiated in accordance with NICE guidance. In TREC 1/28 standard TME surgery cases developed distant recurrence, there was no local recurrence (unpublished data). In GRECCAR 2 local and distant recurrence was recorded in 4 and 13 /71 standard surgery cases respectively). (51)

Safety of pelvic radiotherapy combined with local excision

Although these results show some promise, standard treatment of early rectal cancer does not generally incorporate either radiotherapy or chemotherapy treatment. Therefore, although an organ saving approach may decrease the morbidity and long-term functional consequences associated with TME surgery, it adds the morbidity and long-term functional effects of radiotherapy and chemotherapy. This is particularly pertinent for those patients, perhaps 30%, who do not achieve an adequate response to (chemo)radiation and must convert to TME surgery.

The ACOSOG Z6041 trial reported high levels of acute toxicity using the initial planned doses of radiotherapy and chemotherapy (oxaliplatin and capecitabine).(45) Dose modifications of the chemotherapy and radiotherapy did not completely solve this particular problem and a further 26 patients were recruited before the study was closed. In CARTS 2/55 patients suffered mortality associated with CRT, however, this is likely to reflect the small sample size as larger phase III studies consistently deliver mortality rates of less than 0.5-1%.(53)

CRT in combination with local excision in one small study reported faecal incontinence rates of 46% and faecal urgency in 49% of patients.(54) These rates are similar to historical controls treated by TME without neoadjuvant therapy. Yet, in another study a comparison of TEM only versus TEM after CRT found no difference in faecal incontinence.(55) The TREC study suggested that SCRT and TEM was well tolerated. It is thus important to consider that the addition of neoadjuvant treatment to local excision may be associated with increased toxicity. Patients with poor responses to CRT or SCRT will be the most disadvantaged as they will endure all the downsides of multimodality treatment, including a potentially higher rate of non-sphincter preserving salvage surgery, without experiencing any benefit. The cost of failed organ preservation was highlighted by GRECCAR 2. Carefully conducted prospective and comparative studies are therefore required in order to further refine and optimise organ saving treatments for early rectal cancer.

1.1.7. Key developments for organ preservation treatment in STAR-TREC

The **STAR-TREC** group set out a long-term plan to refine and evaluate organ preservation strategies that utilised (chemo)radiation and selective transanal microsurgery in early rectal cancer.(56) This international collaboration aims to deliver a practice changing study consisting of two parts: (i) an initial feasibility study (completed October 2019) and (ii) follow-on phase III study (current study). The feasibility study described a clear path to phase III by way of a major ethical amendment. The **STAR-TREC** protocol set out a pre-specified plan to retain patients from the feasibility stage and continue recruitment by way of an amendment to the existing protocol. Key refinements in the organ preservation treatment schedule were introduced into clinical practice through the feasibility study.

Radiotherapy fields risk adapted for early rectal cancer

Historically in rectal cancer, the large radiotherapy target volumes have not been adapted to the primary tumour stage. Typical target volumes have incorporated the primary tumour and any gross disease, with elective irradiation of the whole mesorectum, the presacral and internal iliac node with cranial limits around the level of the sacral promontory all receiving the same dose fractionation. An analysis of the patterns of failure of non-irradiated patients in the Dutch TME trial demonstrates that nearly all of the local recurrences were found below the level of the S2/3 interspace.(57)

In early rectal cancer the risk of pelvic lymph node involvement or distal mesorectal nodal involvement is very low.(58, 59) It is thus doubtful that such large elective irradiation volumes are indicated in early rectal cancers especially as most will be clinically node negative and microscopic disease will be predominantly confined to the mesorectum. It is therefore reasonable to reduce the target volume to the peritumoural region of the primary tumour and the mesorectum for future studies.(60) This would lead to a significant volume reduction in the caudal direction and avoidance of the obturator nodes anteriorly, thus decreasing treatment-related toxicity without compromising oncological outcomes.

STAR-TREC has introduced smaller radiotherapy target volumes (50%), risk adapted for early stage rectal cancer. We will also compare contrasting radiotherapy schedules to define the optimal organ preserving strategy for early stage rectal cancer in terms of effectiveness, toxicity (clinician- and patient-reported) and Health-Related Quality of Life (HRQoL). Mesorectal CRT sets out to achieve high rates of CR and reduce requirement for transanal

microsurgery while mesorectal SCRT might achieve lower rates of CR leading to a greater use of transanal microsurgery.

Introduction of watch and wait for complete response

One of the challenges of an organ saving strategy is accurate evaluation of clinical complete response following radiotherapy treatment. Published recommendations for clinical response assessment following radiotherapy have varied between different authors with variability in clinical and pathological complete response concordance.(42, 61, 62) Limited prospective data has been gathered on this subject while the multiple retrospective series are generally confounded through use of early timepoints that do not allow sufficient time for macroscopic and microscopic changes in the tumour to become fully apparent. A retrospective study evaluating the clinical criteria used by Habr-Gama for CR found a low sensitivity of 26% only, 97% specificity and 27% false positive rate of predicting a pathological CR.(63) Using these criteria, 66% of ypT0 patients would not be considered a clinical CR due to residual mucosal abnormalities. The ACOSOG Z6041 trial defined CR as complete disappearance of tumour on proctoscopic examination. They reported 85% sensitivity, 67% specificity and 33% false positive rate for predicting a pathological CR, when local excision was performed 9-13 weeks following the start of CRT.(45) These results suggest that proctoscopic evaluation to determine the presence of residual mucosal abnormalities may be insufficient. The viability of tumour cells seen at the designated time points remains a matter of speculation. Although endoscopic biopsy would allow histopathological examination of response, retrospective series demonstrate poor accuracy in predicting pathological CR (< 25%) possibly due to sampling errors and poor patient selection.(64, 65) Combining several assessment modalities can increase accuracy though at the expense of lower sensitivity.(64) For any organ saving strategy, a carefully designed follow-up protocol is needed to ensure early detection of tumour regrowth or recurrence. MRI assessment of tumour regression grade (mrTRG) may enable identification of more patients with complete response or near complete response and may complement conventional clinical assessment. More work needs to be carried out to determine the added value of mrTRG following radiotherapy for early stage rectal cancer.

STAR-TREC introduced a standardised 2-step radiotherapy response assessment over a much longer 5-month period, delaying the timing of assessment to allow more consistent identification of CR. This extended period provides sufficient time for complete tumour regression to occur and also enables resolution of confounding factors related to treatment such as mucosal oedema or ulceration. Standardisation of CR assessment has enabled

introduction of non-operative management for patients with CR. The **STAR-TREC** Data Monitoring Committee (DMC) reported that they were satisfied with the safety of this approach in December 2018.

Selective local transanal microsurgery

TEM is reserved for patients who are judged to have a partial response to (chemo)radiation. No transanal microsurgery is performed before 5 months to optimize histopathological downstaging and reduce unnecessary conversion to radical TME surgery. Conversion to TME surgery will be advised for ≥ ypT2 disease (following local excision).

Biomarker research (introduced in phase III)

We will investigate genomic markers in blood samples (ctDNA) associated with persistence of tumour tissue following organ preserving treatment. We will specifically evaluate the utility of ctDNA for determination of partial versus complete clinical response, and the decision to proceed to perform local transanal excision. We shall subsequently evaluate the use of serial ctDNA measurement for early identification of failure of organ preservation treatment, and the decision to convert to standard radical surgery.

In addition we will evaluate the utility of genomic markers present in pre-treatment tumour biopsies for prediction of sensitivity to radiation therapy in collaboration with CRUK/MRC S-CORT programme (https://www.s-cort.org/) in order to inform patient selection for an organ preserving approach.

1.1.8. Salvage surgery after organ saving

Salvage radical surgery adhering to the principles of TME is considered the primary treatment for all tumour regrowth in **STAR-TREC**. It is anticipated that with effective surveillance any regrowth or recurrence will predate the development of symptoms. Local regrowth or recurrence may be detected on clinical examination, endoscopic assessment or surveillance MRI. Most local regrowth or recurrence occurs within 24 months but there is evidence to suggest delayed presentation is also possible.(66) Confirmation of recurrent disease in routine clinical practice commonly includes the use of Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scan, which in addition may offer valuable information regarding disease status outside of the primary site of cancer. Recent data suggests that the majority of intraluminal recurrences can be salvaged.(47)

Surgery for regrowth after complete clinical response

Radical resection should be considered as primary treatment for tumour regrowth. This may present as luminal regrowth and/or extraluminal nodal disease. In cases of suspected extraluminal recurrence establishing histological confirmation of tumour regrowth prior to surgery may be difficult and FDG-PET scanning is useful. Some patients may refuse a radical surgical salvage procedure despite the clinicians' recommendation. Where histopathology indicates that salvage with local excision is likely to be adequate treatment, patients may resume an organ-preserving approach under close surveillance. (67)

The Sao Paulo group reports the greatest experience of radical surgery after organ-preserving approach with radiotherapy.(40) In this report 183 patients (cT2-T4) were treated with CRT (50.4-54Gy). Of 90 patients (46%) with a complete clinical response, 28 (31%) had subsequent regrowth. Twenty-six underwent salvage surgery, resulting in overall disease control in 94%. Given that this population included advanced cancers, there would be an expectation that these outcomes would, at the very least, be matched in **STAR-TREC**.

Operative planning of radical surgery should be assessed with reference to pre-treatment MRI staging and also in the context of any local transanal microsurgery to ensure that radical surgery by anterior resection or abdomino-perineal resection will achieve clear margins. If this is not the case then consideration should be given to extended resection, beyond the TME plane.

Surgery for recurrent disease after (chemo)radiation and local excision

Previous local excision is likely to distort the mesorectum and this may make interpretation of recurrent disease difficult, particularly in areas where the mesorectum is thin, typically over the levator muscles and anteriorly adjacent to the prostate and seminal vesicles in the male and vagina in females. Uncertainly over margin involvement on preoperative imaging in this group of patients may require multivisceral resection, or use of extralevator abdominoperineal resection in preference to restorative anterior resection.

Historical reports describing outcomes following radical surgery for recurrence after local excision indicate that R0 resection was possible in only 50% of cases, and long term survival in approximately 25%.(68, 69) Careful surveillance of patients using modern techniques allows earlier detection of relapse. De Graaff et al showed that in 11/12 cases resection margins were free from tumour following standard (rather than extended) TME surgery.(70) In 2015, a review of 27 cases suggested that extended resection was required in 22% of cases,

achieving R0 resection in 93% of cases.(71) Five year overall survival was 50%, and re–recurrence-free survival was 47%. Within the context of **STAR-TREC**, close surveillance is expected to detect recurrent disease at an early stage, amenable to standard resection in the majority of cases.

1.1.9. Transition from STAR-TREC phase II to phase III study

The phase II of the **STAR-TREC** study evaluated the feasibility of accelerating recruitment to an international three arm randomised trial. It was designed to achieve a recruitment rate that would provide confidence that extension into a phase III trial was achievable.

The **STAR-TREC** phase II feasibility component incorporated a three-way randomisation between (a) standard radical surgery versus (b) organ preservation using mesorectal CRT and selective transanal microsurgery versus (c) organ preservation using mesorectal SCRT and selective transanal microsurgery.

The original protocol described a pre-specified plan to retain patients from the phase II stage and continue recruitment rolling into the phase III component by way of a major amendment.

The defined feasibility criteria for success set out for extending the study into a phase III were:

(i) achievement of recruitment targets of 4 patients internationally per month in year 1, rising to 6 patients per month in year 2,

(ii) at least one international partner securing funding and opening the phase II study

(iii) the organ preservation rate of patients recruited to the phase II study and randomised for an organ preservation strategy in year 1 should exceed 50%.

Following their meeting in November 2018 to review the trial progress, the **STAR-TREC** DMC confirmed that all feasibility targets for the pre-planned phase III study had been met.

When transitioning to phase III, the STAR-TREC study design will also be amended. We will dispense with the three-way randomisation (incorporating standard radical surgery) utilised in the phase II feasibility study to introduce a new partially randomised patient preference study design. Patients will now **not** be required to randomise between standard radical surgery and organ preservation treatment. Instead they are able to express a preference for either standard surgery or the organ preservation approach. Those who prefer organ preservation will randomise 1:1 between (i) organ preservation with mesorectal CRT *versus* (ii) organ preservation with mesorectal SCRT to determine the most effective and least

toxic organ saving strategy (Figure 1). Those who prefer standard surgery or have no preference, will undergo standard TME surgery without neoadjuvant radiotherapy treatment. It should be noted that the treatment pathways remain unchanged. The rationale for this change is discussed in section 1.2.1.

The new trial design will be implemented as soon as protocol version 4.0 receives all necessary regulatory approvals.

1.1.10. Summary

Introduction of bowel cancer screening is associated with a significant increase in the incidence of early stage rectal cancer. Radical total mesorectal excision is the highly effective standard treatment for rectal cancer but is associated with significant morbidity and may be over-treatment for these low risk cancers. There is an urgent need for a phase III trial to establish the optimal organ saving approach for early stage rectal cancer. Such a study will provide the high level evidence required to inform clinical practice worldwide. **STAR-TREC** is an international rolling phase II/III trial with a partially randomised patient preference design. The phase II feasibility study evaluated whether it was possible to accelerate patient recruitment from 2 per month, as attained in the previous TREC study, to 6 per month over a two-year period. Following achievement of this objective, this study will roll into the phase III component to evaluate whether either a CRT or SCRT organ-saving strategy is superior in terms of achieving organ preservation, requirement for further surgery, treatment related toxicity, health-related quality of life, and other outcomes; and whether either or both organ-saving strategies lead to an acceptable rate of organ preservation of at least 50%.

1.2. Trial Rationale

1.2.1. Justification for design

Results from small single arm phase II trials support further evaluation of organ preserving treatment strategies for early rectal cancer. These organ preserving strategies should ideally be compared to radical TME surgery which represents the current standard of care for patients with rectal cancer, however most patients show strong preference for organ saving approaches. The optimal method of organ saving is yet to be defined. Current techniques utilise either short course radiotherapy (5 consecutive days treatment) or concurrent fluoropyridine based CRT (5 weeks treatment). ESMO guidelines consider standard CRT to

incorporate oral capecitabine combined with a radiotherapy dose of 46-50.4Gy.(72) Radiotherapy is routinely followed by TEM, to remove the portion of bowel wall affected by cancer.

While published evidence certainly supports further evaluation of organ saving in patients with early stage rectal cancer utilising either SCRT or CRT followed by transanal microsurgery, it has become clear that not all patients actually require surgery. In a significant proportion there are no signs of residual tumour following radiotherapy alone, this is termed a complete response (CR). These patients are likely over treated by routine transanal microsurgery and may be better served by a simple "watch and wait' approach. This issue was reviewed in January 2015 by a member of our trial team.(60)

Justification for amended study design is based upon the overriding views of patients who have entered STAR-TREC, outputs from patient and public involvement workshops, responses from sites and the recent recognition that it would be futile to attempt to measure a difference in unsalvageable pelvic relapse between organ preservation and standard surgery in light of data from the TREC study and a larger group of trials that evaluated CRT and local transanal surgery in early rectal cancer (Table 1). The original three-arm design was initially conceived to measure differences in unsalvageable pelvic relapse as a primary, practice changing endpoint. Emergence of more mature organ preservation data (including our own TREC study) has demonstrated very low rates of pelvic failure; in the order of 5%, and the majority of these cases are salvageable.(46, 48, 51) These figures contrast markedly with our first experience of organ preservation in early rectal cancer utilising local excision alone (no radiotherapy) where local treatment failure was much more common; 18% of T1, 29% of T2 and 50% of T3 tumours.(50, 73) It is no longer logical to evaluate the risk of pelvic failure for standard surgery versus organ preservation as a primary outcome in **STAR-TREC** as the predicted event rate is actually very low. We will instead determine the optimal organ preserving strategy for early stage rectal cancer in terms of effectiveness, toxicity (clinician- and patient-reported) and HRQoL; (i) mesorectal CRT is a dose intense regime that sets out to achieve high rates of CR and avoid transanal microsurgery versus (ii) mesorectal SCRT might achieve lower rates of CR leading to more liberal use of transanal microsurgery. This approach is consistent with that taken to introduce organ preservation as first line treatment for anal cancer, in that patients were not required to accept randomisation to radical surgery (74). From a pragmatic viewpoint it is clear that patients who have consented to randomisation between organ preservation and standard surgery in the feasibility study, did so to try and obtain organ preserving treatment. Participating in the **STAR-TREC** research study has been

the only way of receiving this novel treatment. Of 30 sites that responded to our phase III questionnaire 28 believed that the partially randomised patient preference design would be welcomed by patients and facilitate recruitment.

1.2.2. Justification for participant population

We propose to study patients with relatively early stage disease including TX, T1 and T2 and T3 tumours with up to 5mm of extramural spread (beyond the muscularis propria). Exclusion criteria are designed to avoid including patients with known risk factors for locoregional relapse following rectal cancer treatment.

1.2.3. Justification for capecitabine dosing

There is no international standard dosing for the combination of capecitabine with long course radiotherapy. The phase II CARTS trial used 825mg/m^2 bd seven days per week combined with 50Gy in 25 fractions but the trial management group consensus was that a five days per week dosing regimen was preferred for STAR TREC. A non-inferiority trial compared 5FU with capecitabine 825mg/m^2 seven days per week dosing and found no difference in outcome.(75) The NSABP R04 trial initially used 825mg/m^2 bd seven days per week but following a review of toxicity reduced to five days per week dosing in keeping with our chosen dosing.(76)

1.2.4. Justification for schedule of assessments

The published literature supports use of multi-modality (chemo)radiotherapy and transanal microsurgery as an alternative to radical surgery for curative treatment of early rectal cancer. The long term impact of organ saving treatment upon quality of life and, more importantly, oncological outcome is unknown. A trial is therefore necessary to compare available organ saving treatments with standard surgery. The results of such a trial could be practise changing for the treatment of early rectal cancer patients.

In addition, while it seems probable that a strategy of organ saving may produce substantial benefits over conventional radical surgery, the optimum organ saving treatment schedule remains unclear. Phase II studies suggest that SCRT may have the lowest acute toxicity while CRT may achieve the highest clinical complete response rates. **STAR-TREC** is therefore an international, multi-centre, partially randomised, patient preference rolling phase II/III study

comprising a 1:1 randomisation for eligible subjects with a small, clinically localised rectal cancer choosing an organ preservation approach between:

(1) Organ saving with chemoradiotherapy ± transanal microsurgery

(2) Organ saving with short course radiotherapy ± transanal microsurgery

The study will also include a standard TME radical surgery (non-randomised) comparator arm encompassing reconstructive (low anterior resection) and non-reconstructive (abdominoperineal excision, low Hartmann's procedure) approaches.

Organ saving incorporates two assessments of radiotherapy response at 11-13 and 16-20 weeks. *Note that all timings refer to the* **START** *of (chemo)radiotherapy treatment rather than its completion.* This is to facilitate fair comparison of the differing radiotherapy schedules. Initial assessment at 11-13 weeks (MRI and endoscopy) will identify a small proportion of cases where radiotherapy has had little or no impact upon tumour dimensions. Non-responding patients will be advised to convert to radical TME surgery. Meanwhile individuals whose tumours demonstrate a satisfactory response at this time point will be examined once again at 16-20 weeks (endoscopy) to determine if a complete response (CR) has occurred. It is intended that this interval between assessments will allow for additional tumour regression and resolution of post radiotherapy oedema, facilitating more precise diagnosis of CR.

Radiotherapy response will determine subsequent treatment. **ALL PATIENTS MUST BE ALLOCATED TO ONE OF THREE TREATMENT GROUPS BY WEEK 20**:

(1) Poor response assessed at 11-13 weeks – **patient recommended to convert to radical TME surgery**. This interval was found to be safe in both the TREC and CARTS phase II studies with no patients progressing following radiotherapy treatment. Meanwhile cases that have responded well will be evaluated again at 16-20 weeks.

(2) Complete response (CR) assessed at 16-20 weeks – the bowel wall has reverted to normal and patients are **treated by watchful waiting**. Introduction of this watch and wait strategy for CR is a new development for the TREC and CARTS groups. The Trial Management Group (TMG) feels that initial implementation of watch and wait should be closely monitored within a clinical trial.

(3) Clinically satisfactory, yet incomplete tumour response at 16-20 weeks – the presence of any residual mucosal or bowel wall abnormality suggestive of persisting tumour will prompt **local excision by TEM or equivalent transanal surgical technique**.

2. Aims, Objectives and Outcome Measures

2.1. Aims and Objectives

Phase II

The aim of the **STAR-TREC** phase II study was to assess the feasibility of successfully recruiting to a large, multi-centre randomised trial comparing radical surgery versus organ saving treatment using (chemo)radiotherapy followed by selective transanal microsurgery.

Phase III

The aims of the **STAR-TREC** phase III study are to evaluate whether (a) either a CRT or SCRT organ-saving strategy is superior in terms of achieving organ preservation, requirement for further surgery, treatment related toxicity, health-related quality of life, and other outcomes; (b) either or both organ-saving strategies lead to an acceptable rate of organ preservation of at least 50%.

2.1.1. Primary objective

Phase II:

RECRUITMENT – the **STAR-TREC** phase II feasibility study will evaluate whether it is possible to accelerate patient recruitment from 2 per month, as attained in the previous **TREC** study, to 6 per month over a two-year period. This would demonstrate deliverability of a phase III trial incorporating around 400 patients to evaluate differences in pelvic relapse rates between organ saving and standard surgery. Randomising 70-80 patients per year in phase III would achieve this target in 4 years.

Year 1: randomise 4 cases per month internationally (n=48)
Year 2: randomise 6 cases per month year 2 (n=72).

Phase III:

The **STAR-TREC** phase III study will evaluate whether a CRT or SCRT organ preservation strategy leads to higher organ preservation rates and should become first line treatment for early rectal cancer. This objective can be divided into two main questions:

a. Determine the optimal radiation schedule to achieve the highest rate of organ preservation

b. Determine the optimal radiation schedule to achieve the best quality of life after organ preservation

2.1.2. Secondary objectives

Phase II:

1. **Year 1:** Can one international partner procure independent **STAR-TREC** funding? Successful international collaboration will be necessary to deliver a future phase III study of 400 patients.
2. **Year 1:** Can one international partner open the **STAR-TREC** study to recruitment?
3. **Efficacy of organ preserving treatment arms on completion of phase II study:** Is the organ saving rate > 50% at 12 months (following randomisation) in the experimental arms? This figure is intended as a guide to both the **STAR-TREC** DMC and any phase III peer review.
4. We expect that the actual organ saving rate would lie between 60-70%. Using a target of 50% in phase II will allow for the relatively small sample size. We consider that this metric of efficacy for organ preservation would be suitable for early publication (with toxicity data) as it does not constitute a primary outcome for phase III.
5. Proportion of patients undergoing primary TME surgery (control-group) accurately staged by MRI and satisfying **STAR-TREC** inclusion/ exclusion criteria. We will report the accuracy of MRI based patient selection, compared to the reference standard of post-operative histological staging.
6. Estimate accuracy of MRI assessment for prediction of tumour response to radiotherapy in the organ saving (experimental) group. We will report the proportion of patients reported as achieving 'satisfactory' versus 'poor' tumour response following radiotherapy treatment, based upon assessment of the MRI tumour regression grade (mrTRG). We will also report correlation between mrTRG and histopathological stage for subjects who progress to surgery following radiotherapy; either transanal micosurgery or radical TME.
7. Pelvic failure rate associated with organ saving treatment versus primary TME surgery at 3 years. We consider that organ saving treatment has failed when a tumour recurrence or tumour regrowth is not satisfactorily treated by TME surgery. Treatment failure is defined as the presence of any one of the following three situations:
    - Detection of unresectable pelvic tumour
    - Pelvic tumour that requires beyond TME surgery

- Resected tumour recurrence or regrowth ≤1mm from the circumferential surgical margin after TME surgery

This metric is intended to describe the proportion of patients who are markedly disadvantaged as a consequence of adopting an organ saving approach. This outcome measure will be pivotal in challenging current clinical practice and it is our intention that it becomes the primary endpoint in phase III.

8. Overall survival rate at 3 years associated with organ saving treatment versus primary TME surgery at 3 years.
9. Proportion of patients (in each group) with a stoma at 30 days and 12 months.
10. Health Related Quality of Life (HR QoL) measured by EORTC QLQ CR29 & C30, EuroQoL EQ-5D (baseline and 12, 24 months post randomisation).
11. Bowel, bladder and sexual dysfunction measured by LARS score and ICIQ-MLUTS (baseline and 12, 24 months post randomisation).

Phase III:

- Demonstrate efficacy and low toxicity of mesorectal radiation fields for treatment of early rectal cancer.
- Establish safety of mesorectal radiation and selective transanal microsurgical excision for organ preservation in early rectal cancer.
- Introduce standardised scheme for evaluation and interpretation of clinical response to (chemo)radiation treatment in early stage rectal cancer.
- Establish the safety and efficacy of non-operative management of CR in the context of early rectal cancer treatment.
- Compare the toxicity and quality of life outcomes for patients undergoing standard TME surgery with those who receive organ-preserving treatments.
- Investigate the potential of genomic markers in blood (ctDNA), associated with persistence of tumour tissue, to facilitate the selection of patients for an organ saving approach based upon the likelihood of treatment success.
- Evaluate the utility of ctDNA for determination of partial versus complete response, and thereby the decision to perform local transanal excision.

2.2. Outcome Measures

2.2.1. Primary outcome measure

Phase II:

The primary endpoint of the **STAR-TREC** phase II feasibility study is:

- **RECRUITMENT RATE** - measured at 12 and 24 months. Target recruitment rates are ≥4 and ≥6 patients randomised per month at 12 and 24 months respectively for total accrual of 120 international cases. Each individual country will attempt to exceed the minimum recruitment required to sustain phase III (UK 75, the Netherlands 75, Denmark 30). If recruitment is on target in year two then consideration will be given to an early application for transition to phase III with a funding application and a formal protocol amendment.

Phase III:

The primary endpoint of the **STAR-TREC** phase III study is the proportion of patients with successful organ preservation at 30 months from the start day of (chemo)radiotherapy treatment. This endpoint will be assessed for patients who prefer organ preservation and is defined as an in-situ rectum (includes patients subject to transanal local resection), no defunctioning stoma and an absence of active loco-regional cancer failure. The expected incidence of this outcome is approximately 60%.

2.2.2. Secondary outcome measures

Phase II:

The core secondary endpoints of the **STAR-TREC** phase II trial are:

- Procurement of **STAR-TREC** funding by one international partner
- Opening of **STAR-TREC** by one international partner
- Efficacy of organ preserving treatment arm on completion of phase II study: Is an organ saving rate > 50% at 12 months (following randomisation) achieved in the experimental arms?

Additional outcome measures pertinent to a future phase III study examining the safety and efficacy of organ saving versus standard surgery will also be collected.

- **SAFETY**

- Accuracy of MRI in predicting **STAR-TREC** eligibility
- 30-day mortality
- 6 month mortality
- Surgical morbidity
- Rate of tumour recurrence or regrowth within the bowel wall (experimental arm)
- Rate of tumour recurrence within the mesorectum (experimental arm)
- Rate of distant metastases
- Pelvic failure rate: expressed as a sum of the following (i) unresectable pelvic tumour, (ii) cases requiring beyond TME surgery or (iii) tumour recurrence or regrowth ≤1mm from the circumferential surgical margin after TME surgery.
- Bowel, bladder and sexual dysfunction (measured by EORTC QLQ CR29 & C30, LARS score and ICIQ-MLUTS/ICIQ-FLUTS)

- **EFFICACY**
  - Proportion of patients with/ without a stoma at 30 days and one year
  - Histopathological assessment of tumour down-staging following radiotherapy according to depth of tumour invasion and the incidence of other high-risk features in comparison to non-irradiated (control) group
  - Proportion of patients identified by clinical and MRI assessment as suitable for active monitoring
  - Conversion rates from organ saving to radical surgery
  - Disease free survival
  - Quality of life (measured by EORTC QLQ CR29 & C30, EuroQol EQ-5D, LARS score and ICIQ-MLUTS/ICIQ-FLUTS)
  - Overall survival

Phase III:

A) Secondary outcomes for the randomised comparison between organ-preserving strategies:

- Clinician-reported acute treatment related toxicity up to 30 days following completion of (chemo)radiotherapy
- Proportion of patients with CR to (chemo)radiation therapy
- Proportion of patients undergoing transanal local excision
- Time to event of organ loss assessed for patients who prefer organ preservation; defined as the length of time from the start date of trial treatment until TME surgery

- Non-regrowth pelvic tumour control to 36 months; defined as the length of time from the start date of trial treatment until death (any cause) or development of unequivocal pelvic recurrence **but not including** patients who developed local regrowth which was resected with clear margins using standard TME surgery
- Metastasis free survival to 36 months; defined as the length of time from the start date of trial treatment until death (any cause) or detection of distant metastasis
- Non-regrowth -disease free survival to 36 months; defined as the length of time from the start of trial treatment until death (any cause), detection of local pelvic recurrence or distant metastasis **but not including** patients who developed local regrowth which was resected with clear margins using standard TME surgery
- Overall survival to 60 months defined as the length of time from the start date of trial treatment until death (any cause)

B) Secondary endpoints for analyses incorporating the non-randomised standard surgery comparator:

- Clinician-reported acute treatment related toxicity up to 30 days following completion of (chemo)radiotherapy or date of initial surgery
- Non-regrowth pelvic tumour control to 36 months; defined as the length of time from the start date of (chemo)radiotherapy or date of initial surgery until death (any cause) or development of unequivocal pelvic recurrence **but not including** patients who preferred organ preservation and developed local regrowth which was resected with clear margins using standard TME surgery
- Metastasis-free survival to 36 months; defined as the length of time from the start date of trial treatment or date of initial surgery until death (any cause) or detection of distant metastasis
- Disease-free survival to 36 months; defined as the length of time from the start date of trial treatment or date of initial surgery until death (any cause), detection of local pelvic recurrence or distant metastasis **but not including** patients who developed local regrowth which was resected with clear margins using standard TME surgery
- Overall survival to 60 months defined as the length of time from the start date of trial treatment or date of initial surgery until death (any cause))
- Decision regret at 12 and 24 months

C) Secondary endpoint for analyses of patient-reported outcomes including symptomatic toxicity and health-related quality of life (HRQoL)

In order to perform analyses on patient-reported symptomatic toxicity, health economics and HRQoL, patients will be asked to complete the following questionnaires at baseline (after informed consent is obtained but before trial entry) and 3, 12, 24 and 36 months after the start of trial-specific treatment:

- European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 — This is a 30-item questionnaire developed by the European Organization for Research and Treatment to assess generic aspects of QoL of cancer patients; such as physical, psychological and social functions. It is composed of 5 multi-item scales (physical, role, social, emotional and cognitive functioning) and 9 toxicity related single items.(77)
- EORTC QLQ-CR29 – The Colorectal Cancer Module developed by the European Organization for Research and Treatment (EORTC QLQ-CR29) is used in conjunction with the EORTC QLQ-C30 to assess quality of life in patients with colorectal cancer.(78, 79)
- EuroQoL EQ-5D-3L - The EQ-5D-3L collects information about five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and is the standard questionnaire used in health economic evaluation. The results can be combined into a 5-digit number that describes the patient's health state which in turn can be assigned a utility score. The questionnaire also includes a visual analogue scale to record the patient's self-rated health on a vertical visual scale.(80)
- ICIQ-MLUTS - The International Consultation on Incontinence Modular Questionnaire on Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) is a questionnaire for evaluating male lower urinary tract symptoms and impact on quality of life composed of 13 items which was derived from the fully validated ICSmaleSF questionnaire.(81)
- ICIQ-FLUTS – The International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) is a validated questionnaire for evaluating female lower urinary tract symptoms and impact on quality of life composed of 12 items which was derived from the fully validated BFLUTS-SF questionnaire.(82)
- Low Anterior Resection Syndrome (LARS) Score - A validated, concise and easy-to-use questionnaire for assessment of bowel dysfunction following a sphincter-preserving low anterior resection with or without radiotherapy for rectal cancer. The results

distinguish 3 clinically meaningful severity categories ("no LARS," "minor LARS," and "major LARS").(83)

Analysis of patient-reported symptomatic toxicity and HRQoL health-related quality of life at 3, 12, 24 and 36 months compared to baseline will be conducted incorporating the following comparisons:

- Randomised comparison between organ-preserving strategies
- Non-randomised comparison between organ preserving strategies and the standard surgery comparator

3. Trial Design and Setting

3.1. Trial Design

STAR-TREC is a rolling phase II/III study comprising the following components:

Phase II component:

The **STAR-TREC** phase II feasibility component is an international, multi-centre, randomised trial, comprising a 1:1:1 randomisation for eligible subjects with a small, clinically localised rectal cancer between:

(a) Conventional TME surgery

(b) Organ saving utilising long course concurrent chemoradiation

(c) Organ saving utilising short course preoperative radiotherapy.

A total of 120 patients will be randomised during phase II (40 patients per arm). Recruitment period will be 2 years.

The phase II component will be closed once approximately 120 patients are recruited and all necessary approvals for protocol version 4.0 implementing the phase III design are obtained.

Phase III component:

The **STAR-TREC** phase III component is an international, multi-centre, partially randomised, patient preference phase III study comprising a 1:1 randomisation for subjects with a small, clinically localised rectal cancer choosing an organ preservation approach between:

(a) Organ saving utilising long course concurrent chemoradiation

(b) Organ saving utilising short course radiotherapy

The phase III study will also include a standard TME radical surgery (non-randomised) comparator arm encompassing reconstructive (low anterior resection) and non-reconstructive (abdominoperineal excision, low Hartmann's procedure) approaches.

During phase III, a total of 300 patients will be randomised internationally to the organ preservation arms. An estimate of 80 patients will be recruited internationally to the comparator standard surgery arm. Recruitment period will be 4 years.

Both Phase II and III components:

For both trial components (phase II and III), radiotherapy response assessment in the two organ saving arms will take place at 11-13 weeks and again at 16-20 weeks. *Note that this treatment timeline is with reference to the* **START** *of (chemo)radiotherapy treatment*. The timing of the initial assessment at 11-13 weeks will capture a small proportion of cases that do not respond to radiotherapy treatment.

Clinical assessment will determine allocation to one of three patient groups:-

(1) Tumour progression or little or no response assessed at 11-13 weeks – patient recommended to crossover to TME surgery. This interval was found to be safe in both the TREC and CARTS phase II studies with no patients progressing on treatment. Responding patients will be evaluated again at 16-20 weeks.

(2) Complete response (CR) assessed at 16-20 weeks – the bowel wall has reverted to normal and patients are treated with watchful waiting. Introduction of this watch and wait strategy for CR is a new development for the TREC and CARTS groups.

(3) Clinically satisfactory, yet incomplete response assessed at 16-20 weeks – the presence of residual mucosal or bowel wall abnormality suggestive of persisting tumour requiring local excision using a single port transanal surgery technique. If TEM surgery reveals adverse histopathology, suggesting particularly high risk of pelvic relapse then subjects will be advised to convert to TME.

3.2. Trial Setting

This is a hospital-based study. Candidates will generally be identified in the endoscopy suite following referral for (i) the investigation of new bowel symptoms, (ii) as part of a personal

bowel surveillance programme or (iii) through national bowel screening. Subjects will then be referred on to either a colorectal surgeon or the colorectal cancer multidisciplinary team (MDT) meeting. Eligibility of all pathology proven adenocarcinomas of the rectum (84) will be confirmed at the MDT meeting.

We shall highlight the study to all endoscopic practitioners, especially those who participate in bowel screening so that the referral pathways are clear. The majority of trial sites are likely to act as 'regional hubs' for the early rectal cancer service, and they would specialise in organ saving techniques. These sites will offer both standard (radical surgery) and novel (organ preservation) treatment arms. We expect that the majority of cases referred to regional centres will complete all treatments at that site. It should be noted, however, that a referring centre **might** still take part in **STAR-TREC** (if they wish) by treating patients allocated to TME surgery. This approach was successfully piloted in the TREC study. Where trials treatments are dispensed across multiple sites it is envisaged that patients would currently travel to the regional hub following diagnosis to confirm eligibility and discuss the study. Future development of regional early rectal cancer networks with dedicated MDT meetings may allow this eligibility process to be streamlined so that patients are not required to physically travel. Representatives of the **STAR-TREC** team at each site will have completed training in planning and delivery of the novel treatment strategies.

4. Eligibility

4.1. Inclusion Criteria

- Biopsy proven adenocarcinoma of the rectum
- MRI-defined ≤T3b (with ≤5mm of mesorectal invasion) rectal tumour or endorectal ultrasound-defined ≤uT3b rectal cancer (optional: in centres where high quality endorectal ultrasound (ERUS) is available or patient unable to tolerate MRI)
- MDT determines that all of the following treatment options are reasonable and feasible: (a) TME surgery, (b) CRT (c) SCRT d) TEM.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- For patients choosing organ preservation only:
  - If female and of childbearing potential, must:
    - Have a negative pregnancy test within 7 days prior to study entry
    - Agree to use adequate, medically approved, contraceptive precautions from trial entry until 6 months after the end of study treatment
  - If non-sterilised male male with a partner of childbearing potential, must:
    - Agree to use adequate, medically approved, contraceptive precautions from trial entry until 6 months after the end of study treatment
- Patient able and willing to provide written informed consent for the study

4.2. Exclusion Criteria

- Concomitant or previous malignancies within 3 years prior to trial entry, except those that in the opinion of the MDT are unlikely to relapse within 3 years or lead to death within 5 years
- Unequivocal evidence of metastatic disease (includes resectable metastases)
  Patients with equivocal radiological lesions (e.g. retroperitoneal, liver, lung) that are not classified as M1 are eligible if agreed by MDT
- MRI node positive (≥N1, defined by protocol guidelines)
  Patients with equivocal radiological findings that are either classified as NX or N0 are eligible

- MRI extramural vascular invasion (mriEMVI) positive (defined by protocol guidelines)
- MRI defined mucinous tumour
- Mesorectal fascia threatened (≤1 mm on MRI or ERUS)
- Maximum tumour diameter > 40mm (either measured from everted edges on sagittal MRI or on ERUS)
- Tumour position anterior, above the peritoneal reflection on MRI or EUS
- No residual luminal tumour following endoscopic resection
- Contraindications to radiotherapy including previous pelvic radiotherapy
- Uncontrolled cardiorespiratory comorbidity (includes patients with inadequately controlled angina or myocardial infarction or arrhythmia within 6 months prior to trial entry)
- Known dihydropyrimidine dehydrogenase (DPYD) deficiency
- Known Gilbert's disease (hyperbilirubinaemia)
- Taking coumarin-derivative anticoagulants (e.g. warfarin) that cannot be discontinued at least 7 days prior to starting treatment or substituted by low molecular weight heparin
- Taking phenytoin or sorivudine or its chemically related anologues, such as brivudine, within 4 weeks of trial entry (see Section 8.3.5 for further details)
- Taking metronidazole at study entry
- Pregnant or lactating women
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Age <16 years (UK), <18 years (other countries)

4.3. Pregnancy and Birth Control for Organ Preservation Patients

Sexually active female patients of childbearing potential choosing organ preservation should be advised to avoid becoming pregnant while receiving treatment with capecitabine and while undergoing radiotherapy.

The risks to the human embryo or foetus from exposure to capecitabine are currently unknown and it should be assumed that capecitabine may cause foetal harm if administered to pregnant women. Radiotherapy can cause miscarriages or a child to be born with

abnormalities.

If a patient or the partner of a male trial patient becomes pregnant during the trial, the **STAR-TREC** UK Coordinating Centre must be informed immediately (See section 10.3 for details on the reporting procedure).

4.3.1. Pregnancy testing

Women of childbearing potential who are at risk of becoming pregnant and choose organ preservation must undergo a pregnancy test within 7 days prior to trial entry. Both urine and serum pregnancy tests are acceptable.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 24 consecutive months (i.e. been amenorrheic in the preceding 24 consecutive months without an alternative medical cause)

4.3.2. Contraceptive advice

Due to insufficient data for the effects of capecitabine and radiotherapy during pregnancy and lactation, patients choosing organ preservation must consent to use one method of effective contraception from trial entry until 6 months post CRT or SCRT.

Acceptable methods of effective contraception for this trial are:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
  - Failure rates indicate that, when used alone, the diaphragm or condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
  - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.

- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur.
- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

It is routine practice to offer sperm banking to male patients prior to pelvic CRT.

4.4. Assessment on Magnetic Resonance Imaging

MRI assessment is key to the evaluation of tumour progression in rectal cancer, particularly the tumour's proximity to the surgical resection margin. Detection of microscopic lymph node metastasis by MRI is much more difficult. There is currently no internationally agreed standard to guide diagnosis of mesorectal lymph nodes involved by the spread of rectal cancer. **STAR-TREC** will recruit patients with small rectal tumours where the rate of mesorectal lymph node involvement is expected to be low. We propose to use pre-existing agreed national standards to define lymph node metastasis and exclude patients from **STAR-TREC**. Randomisation (for all patients during phase II; for patients choosing organ preservation only during phase III) will be stratified by country to account for any bias that this may introduce. We will report the accuracy of MRI based patient selection according to each national standard, compared to the reference standard of post-operative histological staging. **STAR-TREC** will help develop international consensus in MRI reporting of mesorectal lymph node involvement by rectal cancer.

5. Consent

In general, eligibility for **STAR-TREC** will be decided at the MDT meeting following review of clinical data, and standard of care endoscopy, biopsy, MRI and Computerized Tomography (CT) investigations. Following this, a **STAR-TREC** clinician with particular expertise in the treatment of early rectal cancer will review the patient, to ensure that the patient is eligible. This will most often be a surgeon accompanied by a specialist nurse, but can be the (radiation) oncologist as well. The **STAR-TREC** study is usually introduced to the patient at this stage, and they will be given a Patient Information Sheet, although it may be discussed earlier in the patient pathway if a diagnosis of early rectal cancer is thought likely.

The team will consider whether further characterisation of the tumour is required in order to plan treatment. A composite endoscopic and endoluminal ultrasound assessment may be used to ensure that the tumour is properly sited.

Once eligibility has been demonstrated patients will be asked if they wish to consent to take part in **STAR-TREC**. A member of the direct clinical care team will always make the first approach to the patient to let them know about the study. A waiting period according to national regulations should be applied to ensure the patient had sufficient time to consider participation in the trial.

Those patients who are randomised to primary TME surgery during phase II, and those who either show no preference or choose to be registered to the radical TME surgery arm during phase III should then be booked for surgery. Participants who are allocated organ saving treatment during phase II or who choose organ preservation during phase III will be booked to see a clinical oncologist or a radiation oncologist and medical oncologist if appropriate.

All patients will be counselled about their prognosis whichever arm of the trial they are allocated to.

Individuals who do not wish to enter the study will be offered standard treatment, which is primary TME surgery. The experimental organ saving treatment using pre-operative (chemo)radiotherapy will not be used to treat patients considered fit for primary TME surgery outside of this study.

It will be the responsibility of the Investigator (either surgeon or oncologist) to obtain written informed consent for each participant prior to performing any trial related procedure. A Patient Information Sheet will be provided to facilitate this process. Investigators or delegates will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that

participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given adequate time to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions.

If the participant expresses an interest in participating in the trial they will be asked to sign and date the latest version of the Informed Consent Form. The participant must give explicit consent for the regulatory authorities, members of the research team and representatives of the Coordinating Sponsor to be given direct access to the participant's medical records.

The Investigator, or delegate, will then sign and date the form. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File. Once the participant is entered into the trial, the participant's unique trial number will be entered on the Informed Consent Form maintained in the Investigator Site File. In addition, and where national regulations allow, if the participant has given consent a copy of the signed Informed Consent Form will be sent to the UK Coordinating Centre for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the Patient Information Sheet given to participant and version number of Informed Consent Form signed and date consent received.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the Patient Information Sheet and Informed Consent Form will be available from the relevant NCC and for UK sites will be printed or photocopied onto the headed paper of the local institution. Details of all participants approached about the trial will be recorded on the Participant Screening Log. For those UK patients who enter the study and with the participant's prior consent, their medical practitioner (General Practitioner (GP) in the UK) should also be informed that they are taking part in the trial.

6. Trial Entry

6.1. Enrolment

Patients must have biopsy proven adenocarcinoma of the rectum, staged by CT and MRI (and/or in some circumstances ERUS) as ≤T3b. MRI should show no definite evidence of lymph node involvement (i.e. N1), and none of the staging investigations should show definitive evidence of metastatic disease (i.e. M1, even if that metastatic disease is deemed resectable).

The 8th edition of the TNM classification and staging system of malignant tumours (85) with modifications will be used. The term Mx may be used to refer to patients with indeterminate or insufficient evidence of metastasis.

If patients are unable to tolerate MRI then it may be substituted for ERUS. ERUS may also be used to supplement MRI in centres where this is available. **STAR-TREC** clinicians will liaise with the bowel-screening programme to expedite transition of patients from diagnostic to treating services. Hospitals already record rectal cancer outcomes for all patients and so the proportion of eligible patients recruited will be accurately recorded.

In phase III only, participants will be asked to choose either:

(a) Conventional TME surgery

(b) Organ saving approach

Patients showing no preference will be offered to be registered to the conventional TME surgery arm.

Patients showing a preference for organ preservation, will be randomised 1:1 at the time of trial entry to either:

a) Organ saving utilising chemoradiation

b) Organ saving utilising short course radiotherapy

Following informed consent, which will be conducted in accordance with Good Clinical Practice (GCP) standards, confirmation of all eligibility criteria and completion of the baseline assessments, patients will be entered into the **STAR-TREC** study. Trial Entry forms are provided in the **STAR-TREC** Investigator Site File and should be used to collate the necessary information prior to proceeding to trial entry.

6.2. Randomisation during phase II

Participants will be randomised to either:

(a) Conventional TME surgery

(b) Organ saving utilising chemoradiation

(c) Organ saving utilising short course preoperative radiotherapy at the level of the individual on a 1:1:1 basis.

Randomisation will be provided by a computer-generated program at the Birmingham Clinical Trials Units (BCTU). The randomisation programme will use a minimisation procedure with the following variables:

(1) MRI (or ERUS) Tumour staging (≤T3a and ≥ T3b)

(2) Country (UK, the Netherlands, Denmark)

Stratification will be by T stage to ensure that the more advanced tumours are equally represented across treatments; stratification by country will be done to account for any bias arising from the slight differences in pre-treatment MRI based staging assessment (see section 4.4).

To avoid any possibility of the treatment allocation becoming too predictable, a random factor will be included within the algorithm whereby for a proportion of the allocations true randomisation will be implemented rather than by using the minimisation allocation.

6.2.1. Telephone randomisation

During phase II, patients are entered in the trial by telephone call to the BCTU randomisation service. Randomisation notepads are provided in the **STAR-TREC** Investigator Site File for the Phase II trial and should be used to collate the necessary information prior to randomisation. After all the necessary details have been provided, the treatment allocation for the Phase II will be specified at the end of the telephone call. For patients in the UK, the patient's GP should be notified that they are in the **STAR-TREC** study, and a specimen "Letter to GP" is provided for this purpose.

6.3. Trial entry during phase III

During phase III, confirmation of eligibility and trial entry will be conducted on the electronic Remote Data Capture (eRDC).

https://www.cancertrials.bham.ac.uk/STARTREC

Login details will be provided by the trials office.

If the online system is unavailable, emergency trial entry can be done by telephone:

☎ +44 (0) 121 414 3973 or +44 (0) 121 414 7671
9am-5pm Monday to Friday

The following information will be requested by the trial entry wizard:

- Country, National Coordinating Centre (NCC), name of site, Investigator and person registering the patient
- Patient's full name, date of birth, National Health Service (NHS) number (or in Scotland the Community Health Index (CHI)), and hospital number. Patient identifiers may be left blank where international restrictions apply.
- Patient's preference for standard surgery or organ preservation
- Confirmation that the patient is eligible for the trial

For patients choosing organ preservation, randomisation will be provided by a computer-generated program which will use a stratification procedure with the following variables:

(1) MRI (or ERUS) Tumour staging (≤T3a / T3b)

(2) Country (UK / the Netherlands / Others (currently Denmark)

Stratification will be by T stage to ensure that the more advanced tumours are equally represented across treatments. Patients that have both an MRI and ERUS performed will be stratified by the tumour stage reported from the MRI test. Stratification by country will be done to account for any bias arising from the slight differences in pre-treatment MRI based staging assessment (see section 4.4).

To avoid any possibility of the treatment allocation becoming too predictable, a random factor will be included within the algorithm whereby for a proportion of the allocations true randomisation will be implemented rather than by using the minimisation allocation.

At the end of the procedure the patient will be allocated to the appropriate treatment arm and given a unique trial number. A Trial Entry Confirmation Report should be printed and filed in the Investigator Site File.

With the patient's prior consent, their medical practitioner (GP in the UK) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose but it is anticipated that this is translated and adapted in accordance with national practices.

7. Investigational Medicinal Products

7.1. Trial Treatment

The only Investigational Medicinal Product (IMP) used in the **STAR-TREC** study is capecitabine. Only patients randomised to organ preservation using long course concurrent chemoradiation will receive the study IMP.

7.2. Investigational Medicinal Product

7.2.1. Investigational Medicinal Product supply and labelling

Trial supplies of capecitabine for the entire treatment period will be arranged through normal hospital supply arrangements. Participating hospitals will be responsible for the local ordering of their stock of capecitabine, drug costs will not be reimbursed.

Chemotherapy prescriptions should conform to local best practice including electronic prescribing systems where available. The full 5 week course of capecitabine can be dispensed at the start of treatment.

If a dose reduction is required before the end of the 5 weeks course due to toxicities, all remaining capecitabine tablets should be returned, patient weight re-measured and new stock re-dispensed including amended dose details in the dispensing label.

Trial medication will be commercial stock in standard packaging. A country--specific trial label will be applied prior to dispensing.

7.2.2. Dispensing and drug accountability

A trial-specific prescription will be completed by the responsible investigator and will be received by the pharmacist (or designee) prior to dispensing trial medication. Accurate records of trial IMP dispensed, returned and disposed should be maintained on the hospitals local drug accountability logs. Such in-house records must remain available to be submitted to the applicable NCC for review upon request.

For detailed information on the supply, labelling and accountability of capecitabine, please refer to the Summary of Trial Drug Arrangements document in the **STAR-TREC** Pharmacy File.

8. Trial Treatments

8.1. Non-randomised Comparator Arm – Standard Surgery

This will encompass both reconstructive and non-reconstructive approaches to rectal resection using the principles of TME surgery. The former includes low anterior resection, the latter abdominoperineal excision or low Hartmann's procedure. Surgeons may use either minimally invasive i.e. laparoscopic/robotic, open or hybrid (combined minimally invasive and open) approaches to surgery. The quality of surgery will be measured using a standardised histopathological assessment that grades whether surgery was performed according to the principles of TME.

8.2. Organ Saving Experimental Arms (CRT and SCRT): Radiotherapy

The key aspects of the radiotherapy are summarised below. A separate Radiotherapy Planning Document provides illustrated examples of radiotherapy target volume definition, and should be used during the radiotherapy planning and treatment process.

8.2.1. Radiotherapy planning

Radiotherapy planning will comply with ICRU 83. The treatment technique can be either CT planned 3D conformal or intensity-modulated radiotherapy (IMRT).

The use of a planning CT scan with target volumes delineated on each slice and pixel based inhomogeneity correction is considered standard practice and is a mandatory requirement.

Patient set up

It is recommended that appropriate immobilisation and a scan/treatment position is used which the site is familiar with. The supine position is recommended but not mandated.

Contrast

The use of intravenous and oral contrast are optional and should align with local centre policy.

Patient data acquisition

The scan limits are the superior aspect of L5 superiorly to 4cm below a radio-opaque marker indicating the anal verge. The recommended slice thickness is 2-3mm (a maximum of 5mm is acceptable).

8.2.2. Definition of target volumes

The target volume definition process requires the delineation of gross (GTV), clinical (CTV) and planning (PTV) target volumes.

GTV	• All macroscopic tumour is delineated on each slice.
CTV	On each slice, the mesorectal fascia is delineated circumferentially: *Superior limit:* • Is defined as the S2/S3 interspace (determined on the sagittal or scout view on the planning system). • A minimum of 2 cm is required from the superior limit of the GTV 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.) *Inferior limit:* • Is defined as 2 cm inferior to the inferior limit of the GTV. • 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 1cm. (The anal canal is delineated if the CTV extends below the mesorectum.)

	Anterior limit: • The mesorectal fascia is contoured. • If the mesorectal fascia disappears anteriorly, the anterior border is the anterior rectal wall. • For cranial slices with no visible rectum, the anterior border is defined by the contour used for the last cranial slice with visible rectum. *Posterior limit:* • Is defined as the anterior margin of the sacrum or coccyx, or the inner border of the puborectalis muscle in caudal slices. *Lateral limit:* • The mesorectal fascia is contoured. • High pelvis - If the mesorectal fascia disappears laterally, the inner border of the pyriformis muscle is contoured • Mid pelvis - The mesorectal fascia is contoured. • Low pelvis - The inner border of the puborectalis muscle as it converges to form the anorectal ring. Further guidance on the definition of the CTV is provided in the Radiotherapy Planning Document.
PTV	• CTV with a 1cm isotropic margin applied superiorly, inferiorly, posteriorly and laterally, and a 1.5cm isotropic margin applied anteriorly. • If there is no daily on-treatment image-guidance, an additional isotropic margin (according to local policies) for set-up error is to be added.

8.2.3. Radiotherapy treatment

Radiation therapy should be delivered with photon energies ≥6 MV using a linear accelerator. 3D conformal radiotherapy with multileaf collimators or IMRT plans are acceptable. Typically a three or four field arrangement will be used for 3D conformal, and multiple fixed beams or treatment arcs are used for the delivery of IMRT. All fields must be treated during each treatment session.

Total Dose

Short course radiotherapy arm: A total dose of 25 Gy in 5 daily fractions over a total time of 1 week should be delivered, treating 5 days per week, 1 fraction per day, using 5 Gy per fraction.

Long course chemoradiotherapy arm: A total dose of 50 Gy in 25 daily fractions over a total time of 5 weeks should be delivered, treating 5 days per week, 1 fraction per day, using 2.0 Gy per fraction. This will be combined with Capecitabine 825 mg/m^2 bd on radiotherapy treatment days.

Target dose constraints are as below:

Table 2: Target dose constraints

Region of interest	Dose constraints
CTV	$V_{95\%}$ = 100%
PTV	$V_{95\%} \geq 99\%$ $V_{90\%}$ = 100% $V_{105\%} \leq 1\%$

For Organ and Risk (OAR) target dose constraints, please see the separate Radiotherapy Guidelines.

On-treatment set-up verification

The best available positional verification methods should be used which may include electronic portal images compared to digitally reconstructed radiographs (DRRs), or cone-beam CT matching using the planning scan. Acceptable deviations should be assessed according to local policies and the isocentre moved if disagreement is seen in excess of agreed local tolerance levels.

For the short course radiotherapy schedule, daily online correction is recommended.

For the chemoradiotherapy schedule, treatment verification should be performed at least three times during the first treatment week, and at least weekly thereafter. Note that PTV margins will depend on image guidance schedule; see the separate Radiotherapy guidelines for further details.

8.2.4. Quality assurance for radiotherapy

The radiotherapy quality assurance (RT QA) programme for the study will be designed and implemented by the 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 **STAR-TREC** trial will include both pre-trial and on trial components. Attempts will be made to streamline the RT QA processes, where appropriate, with previously completed QA for other clinical trials. Specifically, centres already approved for mesorectal outlining and planning through other trials may not need to complete any further pre- and on-trial outlining and planning QA. All centres using IMRT delivery must successfully complete the IMRT credentialing programme through the National RTTQA group or equivalent.

Please see the Radiotherapy guidelines for full details of the trial radiotherapy QA process.

8.3. Organ Saving Experimental Arm with Concurrent Chemoradiotherapy

Concurrent chemoradiotherapy consists of capecitabine and is administered at a starting dose of 825 mg/m^2 bd on days of radiotherapy treatment (excluding weekend days when patients do not undergo radiotherapy treatment). Side-effects include nausea, vomiting and diarrhoea though management with anti-emetics and loperamide is seldom necessary; bone marrow suppression (leuco- and granulocytopenia, thrombocytopenia, anaemia); and skin toxicity ("hand-foot syndrome" - dry or red skin mainly on hands and feet). Neutropenic sepsis is rare. For scoring of chemotherapy toxicity the CTCAE version 4.03 will be used.

8.3.1. Summary treatment schedule

Table 3: Summary treatment schedule

Week	**1**					**2**					**3**					**4**					**5**				
Days	D 1-5					D 8-12					D 15-19					D 22-26					D 29-33				
Radiotherapy: 50 Gy/25fractions	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Oral capecitabine* **825 mg/m^2** orally bd Mon-Fri x 5 weeks	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

*Capecitabine should be taken on the days of radiotherapy only (normally Monday-Friday). If radiotherapy is not given (e.g. due to bank holiday or machine breakdown, etc.) then capecitabine should not be taken.

8.3.2. Chemoradiotherapy treatment details - chemotherapy

Administration

Pre-chemoradiotherapy treatment, the following criteria must be met:

- Estimated creatinine clearance ≥50 ml/min
- Absolute neutrophil count ≥1.5x10^9/l;
- Platelets ≥100 x 10^9/L
- Serum transaminase ≤3 x Upper Limit Normal/l (ULN)
- Bilirubin ≤1.5 x ULN

Capecitabine is taken orally twice a day in equal doses for 5 days per week (normally Monday – Friday), on the days of radiotherapy administration only, throughout the 5 week course of radiotherapy. If radiotherapy is not given (e.g. due to machine maintenance or bank holiday), then capecitabine should not be given that day either. Capecitabine treatment can begin on any day of the week; however, **there is normally no capecitabine treatment on Saturday or Sunday**, unless radiotherapy is given on one of these days. Patients are asked to swallow whole capecitabine tablets with a glass of water twice each day within 30 minutes after the ingestion of food (ideally after breakfast and evening meals), commencing the morning of the first dose of radiotherapy treatment. Tablets should not be crushed or cut.

It is recommended that patients keep a diary of the number of capecitabine tablets taken to assist site research staff in recording dose delivered on the Case Report Form (CRF).

Dose banding

Dose banding may be used for oral capecitabine. See tables below for proposed protocol dose banding ranges. The NHS capecitabine national dose banding table is considered an acceptable alternative. Sites may use different dose banding used in their electronic prescribing process provided that it is pre-approved for each centre by the UK Coordinating Centre.

Table 4a: Dose banding for the starting dose of oral capecitabine

Starting Capecitabine dose = 825 mg/m² bd		Number of tablets to be taken at each dose (morning and evening) Mon-Fri	
Surface area (m²)*	**Twice daily dose (mg)**	**150 mg**	**500 mg**
≤1.46	1150	1	2
1.47-1.66	1300	2	2
1.67-1.89	1500	0	3
1.90-2.12	1650	1	3
≥2.13	1800	2	3

* Surface area should be calculated using either Mosteller or Du Bois.

Table 4b: Dose banding for reduced doses of oral capecitabine

75% Capecitabine dose = 618.75 mg/m² bd		Number of tablets to be taken at each dose (morning and evening) Mon-Fri	
Surface area (m²)*	**Twice daily dose (mg)**	**150 mg**	**500 mg**
≤1.46	900	6	0
1.47-1.66	1000	0	2
1.67-1.89	1150	1	2
1.90-2.12	1300	2	2
≥2.13	1450	3	2

50% Capecitabine dose = 412.5 mg/m² bd		Number of tablets to be taken at each dose (morning and evening) Mon-Fri	
Surface area (m²)*	**Twice daily dose (mg)**	**150 mg**	**500 mg**
≤1.46	600	4	0
1.47-1.66	650	1	1
1.67-1.89	750	5	0
1.90-2.12	800	2	1
≥2.13	900	6	0

* Surface area should be calculated using either Mosteller or Du Bois.

Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the Principal Investigator, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the Site Signature and Delegation Log.

8.3.3. Management of acute toxicity

Patients should be reviewed at least weekly during CRT to perform an assessment of acute toxicity. However, the local team should have a structure in place that ensures that patients experiencing side effects can be seen and undergo review more often if required to monitor the severity of side effects and take appropriate actions in regards to trial treatment and management of symptoms.

The following guidance should be followed for the management of acute toxicity and dose modifications:

- Adverse Events (AEs) should be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03)
- In the event of overlapping toxicities, dose modification should be based on the worst toxicity grade observed.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken in the CRF and in the medical notes.
- If a patient experiences a toxicity, then dose modifications should be applied as specified in the protocol section 8.3.7.
- **In the event of a second episode of the same grade ≥3 toxicity, capecitabine should be permanently discontinued**.

8.3.4. Support medication

Anti-emetic recommendations

Oral anti-emetics should be used according to local policy as required.

Anti-diarrhoeals

It is recommended that all patients have loperamide prescribed prior to commencement of treatment in case of the development of diarrhoea.

It is strongly recommended that patients are instructed to contact the radiotherapy centre urgently if diarrhoea is not controlled after 12 hours of loperamide therapy.

8.3.5. Concomitant medication

Capecitabine

Precautions: The effects of capecitabine are potentiated when co-administration occurs with warfarin, phenytoin and sorivudine (an antiviral). A review of concomitant medications should be performed at baseline to confirm safety. **Please note that patients who are receiving any of these three drugs are not eligible for this study:**

- Concurrent phenytoin – patients are not eligible for this study
- Concurrent sorivudine or its chemically related analogues, such as brivudine within 4 weeks prior to trial entry – patients are not eligible for this study
- Coumarin-derivative anticoagulants – patients receiving oral warfarin or other coumarin-derivative anticoagulants are eligible for this study with one of the two options listed below according to clinical judgement that is used in routine clinical practice:
  1. Discontinuation of coumarin-derivative anticoagulant at least 7 days prior to commencement of capecitabine treatment and for the duration of CRT (this may be reasonable when given as prophylaxis for patients with atrial fibrillation – this is a local clinician decision)
  2. Conversion from coumarin-derivative anticoagulant 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 capecitabine treatment.

  Warfarin or other coumarin-derivative anticoagulants must not be commenced during CRT. In the unlikely event that this does occur (i.e. commenced without consultation with the oncology team), the warfarin must be immediately discontinued, low molecular weight heparin commenced and an INR performed. The patient management should be discussed with a Clinical Coordinator.

8.3.6. Out of hours medical care

Medical care, including out-of-hours is the responsibility of the site team.

Patients allocated CRT should carry a **STAR-TREC** patient card with emergency and routine contact telephone numbers for the trial team at the radiotherapy centre.

It is recommended that patients allocated CRT experiencing serious treatment-related toxicity are admitted to the radiotherapy centre. If this does not happen the trial team must have daily contact with the treatment hospital and consider transfer to the radiotherapy centre.

8.3.7. Dose modifications and management of toxicity

This section provides guidelines for dose modifications in response to organ function and toxicity for patients allocated CRT. These should be adhered to wherever possible, however, it is acknowledged that trial investigators and treating consultants are likely to have significant experience with the combination of radiotherapy and concurrent capecitabine. Deviations from these guidelines concerning any dose reductions or treatment discontinuation due to toxicities above those recommended by the current capecitabine Summary of Product Characteristics (SmPC) considered in the patients' best interest are therefore permitted and should be recorded in the CRFs and will not constitute a protocol violation.

During CRT treatment, weekly blood samples will be taken and their results used to inform patient management.

Haematological toxicity

Weekly blood samples will be taken during CRT, and chemotherapy and radiotherapy modified as follows:

Table 5: Dose modifications in response to Haematological toxicity

CTCAE Grade	Toxicity	Toxicity event	Action for Capecitabine	Action for Radiotherapy
1	Neutrophils ≥1.5 x 10^9/L or Platelets ≥75 x 10^9/L	Any	Continue at same dose	Continue
2	Neutrophils ≥1.0 – <1.5 x 10^9/L or Platelets ≥50 – <75 x 10^9/L	1st	Interrupt until grade 0 – 1, then resume at 100% dose	Continue
		2nd	Interrupt until grade 0 – 1, then resume at 75% dose	
		3rd	Interrupt until grade 0 – 1, then resume at 50% dose	
		4th	Discontinue permanently	
3	Neutrophils ≥0.5 – <1.0 x 10^9/L or Platelets ≥25 – <50 x 10^9/L	1st	Interrupt until grade 0 – 1 then resume at 75% of starting dose	Interrupt until grade 0 – 1
		2nd	Discontinue permanently	
4	Neutrophils <0.5 x 10^9/L or Platelets <25 x 10^9/L	1st	Interrupt until grade 0 – 1 and if patient considered fit resume with 50% dose	Interrupt until grade 0 – 1
		2nd	Discontinue permanently	

No dose reductions or interruptions are required for anaemia (non-haemolytic) if it can be satisfactorily managed by transfusions or erythropoietin.

In the event of a second episode of the same grade ≥3 toxicity, stop all chemotherapy permanently.

Non-haematological toxicity

Diarrhoea

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 treatment centre. If circumstances prevent this, then this guidance must be rapidly shared with the local treating team and regular contact maintained.**

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

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

Onset of grade 2 diarrhoea:

- Suspend all chemotherapy
- Send stool for culture and *C. difficile* toxin
- Commence loperamide
- Ensure adequate oral rehydration
- Continue with radiotherapy if patient considered fit for treatment
- Daily review

If bowel frequency returns to grade ≤1 and loperamide usage is ≤ 6 mg per day, chemotherapy (and radiotherapy if suspended) can recommence at 75% of starting dose.

Onset of grade 3 diarrhoea or ongoing grade 2 diarrhoea despite above measures:

- Admission of the patient is recommended
- Commence loperamide
- Send stool for culture and *C. difficile* toxin
- Commence intravenous fluids with regular appropriate volumetric assessment
- Suspend all trial treatment (radiotherapy **and** chemotherapy)

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). The regimen used should cover likely enteric pathogens.

If grade 3 diarrhoea is not controlled to 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 BNF guidance and should be reviewed daily
- Closely monitor serum C-Reactive Protein (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

If 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.

[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. Please note the criteria for admission stated above]

Table 6: Dose modifications in response to Diarrhoea

CTCAE Grade	Toxicity	Capecitabine	Radiotherapy
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Continue if ≤ 6 mg loperamide per 24 hours required	Continue
2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; Moderate cramping	Interrupt until grade 0 – 1 and ≤ 6 mg loperamide per 24 hours required; then recommence at 75% of starting dose	Continue as long as patient considered fit for treatment.
3	Increase of ≥ 7 stools per day over baseline; severe increase in ostomy output compared to baseline; limiting self-care Activities of Daily Living (ADL); Severe cramping or peritonism (localised guarding on abdominal examination)	Interrupt until grade 0 – 1 and ≤ 6 mg loperamide per 24 hours required; then recommence at 50% of starting dose. If patient is neutropenic and has sepsis stop permanently.	Interrupt until grade 0 – 1, ≤ 6 mg loperamide per 24 hours required, and patient considered fit.
4	Life threatening consequences; urgent intervention indicated	Discontinue treatment permanently	Interrupt until grade 0 – 1, ≤ 6 mg loperamide per 24 hours required, and patient considered fit.

CRT should only be recommenced when the following criteria are met:

- Bowel function has returned to grade 0/1
- Loperamide usage is ≤ 6 mg per 24 hours
- The patient is considered fit to resume therapy by a trial Investigator
- Dose reductions are applied according to the table above

In the event of a second episode of grade 2 diarrhoea the patient's management should be discussed with a Clinical Coordinator.

In the event of a **second episode of grade 3 diarrhoea** stop all chemotherapy permanently.

Palmar-plantar syndrome

Table 7: Dose modifications in response to Palmar-plantar syndrome

CTCAE Grade	Description	Capecitabine
1	Minimal skin changes or dermatitis (e.g., erythema, oedema, or hyperkeratosis) without pain	Continue
2	Skin changes (e.g., peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting instrumental ADL	Interrupt until grade 0 – 1 then resume at 75% of starting dose
3	Severe skin changes (e.g., peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting self-care ADL	Interrupt until grade 0 – 1 then resume at 50% of starting dose

In the event of a second grade ≥3 episode of the same toxicity, stop capecitabine permanently.

Deranged renal function

The calculated creatinine clearance (using either the Cockcroft-Gault or Wright formula) should be used to estimate Glomerular Filtration Rate (GFR) each week. If less than 50 mL/min then the capecitabine dose should be reduced or stopped according to the table below and an isotope clearance or a formal 24 hour urine collection requested. When this result is available, the capecitabine dose should then be re-adjusted using the table below. If the isotope clearance or formal 24 hour urine collection GFR estimation is higher than the calculated creatinine clearance, then the former will be used and if this result is ≥ 50 mL/min, the patient can be re-escalated to 100% starting dose. The isotope clearance or formal 24 hour urine collection can guide capecitabine dosing in subsequent weeks providing the serum creatinine does not rise by > 10%.

Table 8: Dose modifications in response to deranged renal function

Estimated GFR	Capecitabine
≥ 50 mL/min	Continue at starting dose
30 – 49 mL/min	Reduce to 75% of starting dose
< 30 mL/min	Stop permanently

Deranged hepatic function

The table below describes dose modifications in case of deranged hepatic function which are considered to be related to treatment.

Table 9: Dose modifications in response to deranged hepatic function

CTCAE Grade	Toxicity	Capecitabine	Radiotherapy
1	Elevated bilirubin > 1.0 – ≤1.5 x ULN	Continue	Continue
2	Elevated bilirubin > 1.5 – ≤3.0 x ULN	Reduce to 75% of starting dose	Continue
3	Elevated bilirubin > 3.0 – ≤10 x ULN	Stop permanently	Continue
≥ 2	Alanine Transaminase (ALT) or Aspartate Aminotransferase (AST) > 2.5 x ULN	Interrupt until grade 0 – 1, then recommence at 75% of starting dose	Continue

Fatigue

The table below describes dose modifications in case of fatigue **which is considered to be related to treatment.**

Table 10: Dose modifications in case of grade 3 fatigue, which is considered to be related top treatment

CTCAE Grade	Description	Capecitabine	Radiotherapy
1	Fatigue relieved by rest	Continue	Continue
2	Fatigue not relieved by rest; limiting instrumental ADL	Interrupt until grade 0 – 1, then resume at 100% of starting dose	Continue
3	Fatigue not relieved by rest, limiting self-care ADL	Interrupt until grade 0 – 1, then resume at 75% of starting dose	Interrupt until grade 0 – 1

Vomiting

The table below describes dose modifications in case of grade 3 and 4 vomiting **which is considered to be related to treatment**.

Table 11: Dose modifications in case of grade 3 and 4 vomiting which is considered to be related to treatment

CTCAE Grade	Description	Capecitabine	Radiotherapy
1	1 - 2 episodes (separated by 5 minutes) in 24 hrs	Continue	Continue
2	3 - 5 episodes (separated by 5 minutes) in 24 hrs	Interrupt until grade 0 – 1, then resume at 100% of starting dose	Continue
3	≥ 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalisation indicated	Interrupt until grade 0 – 1, then resume at 75% of starting dose	Interrupt until grade 0 – 1
4	Life-threatening consequences; urgent intervention indicated	Interrupt all treatment and contact the **STAR-TREC** Clinical Coordinator to discuss the patient's management	

Mucositis

Table 12: Dose modifications in response to Mucositis

CTCAE Grade	Capecitabine	Radiotherapy
1	Continue at 100% dose	Continue
2	Interrupt until grade 0 – 1, then resume at 75% of starting dose	Continue
3	Interrupt until grade 0 – 1, then resume at 50% of starting dose	Continue if considered fit for radiotherapy
4	Stop permanently	Stop permanently

In the event of a second grade ≥3 episode of the same toxicity, stop all chemotherapy permanently

Other non-haematological toxicity

The table below describes dose modifications in case of other non-haematological toxicities which are considered to be related to the treatment. Dose modifications should be made to the treatment most likely responsible for the toxicity necessitating the dose reduction.

Table 13: Dose modifications in case of other non-haematological toxicities which are considered to be related to the treatment

CTCAE Grade	Capecitabine	Radiotherapy
1	100%	Continue
2	Interrupt until grade 0 – 1, then resume at 75% of starting dose	Continue
3	Interrupt until grade 0 – 1, then resume at 50% of starting dose	Continue but treat with appropriate supportive therapy
4	Stop permanently	Interrupt until grade 0 – 1 and patient considered fit

8.3.8. Unplanned breaks in radiotherapy

When an unplanned break in radiotherapy occurs (bank holiday, machine breakdown), capecitabine 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 50Gy in 25 fractions) even if this is delivered over a longer treatment time – additional fractions should NOT be given on the same day.

9. STAR-TREC Trial Assessments

9.1. Clinical (chemo)radiotherapy Response Assessment Schedule

Radiotherapy response assessment will be performed as a two-step process. The assessment schedule is defined in relation to **the start** of (chemo)radiotherapy treatment (rather than its conclusion) to enable more direct comparison of radiotherapy response between treatments of different duration. Response assessment is a composite clinical evaluation conducted using digital rectal examination, endoscopy and MRI. Endoscopic photographs and representative MRI images may be reviewed centrally (if deemed necessary / at the discretion of sites) to develop a consistent approach to the assessment of complete response (CR) within **STAR-TREC**. Introduction of a watch and wait strategy for CR without the need for routine TEM surgery to confirm pathological complete response, is a new development for the **STAR-TREC** group.

The **first assessment takes place 11 to 13 weeks** after the start of (chemo)radiotherapy treatment (i.e. 10 to 12 weeks following completion of SCRT and 6 to 8 weeks following completion of CRT). This is a composite clinical, endoscopic and MRI based assessment. The main purpose of the first assessment is to identify a minority of cases where there has been little or no evidence of tumour response to radiotherapy treatment. Such cases are deemed unsuitable for organ saving and patients will be strongly advised to proceed with TME surgery within a 4-week timeframe.

The **second radiotherapy response assessment will be performed at 16-20 weeks.** Patients will have already demonstrated clear evidence of endoscopic downsizing and no features of tumour progression on MRI at the first assessment. The purpose of the second clinical assessment is to identify cases that comply with our protocol definition of CR. In cases where CR is attained, routine TEM may be avoided, and a process of close observation termed watchful waiting is followed instead. Cases that do not comply with our protocol definition for CR at this second assessment will have a full thickness local excision performed by TEM (or equivalent single port transanal surgery technique) to remove the residual mucosal or bowel wall abnormality.

9.1.1. Definition of tumour progression, poor or no response to (chemo)radiation assessed at 11-13 weeks

The presence of **any one of the following criteria** defines tumour progression, poor or no response to (chemo) radiation treatment in **STAR-TREC**:

(1) Using white light endoscopy with phosphate enema (or comparable) bowel preparation. Evidence of residual tumour or marked ulceration with (a) less than 50% reduction in tumour size or (b) residual tumour diameter > 20mm (where this residual mass cannot reasonably be attributed to inflammation, oedema or tumour regression).

(2) Evidence of tumour progression or minimal downsizing using digital rectal examination.

(3) Using high quality MRI and conventional TNM staging, evidence of tumour progression (>ymrT3b, ymrN1+, N1c or EMVI positive).

In the event any one of these criteria are met, the patient will be advised to undergo radical TME surgery within a 4-week timeframe.

mrTRG will also be recorded alongside to explore its potential value in complementing conventional clinical assessments, but it will not be used to guide patient care.

9.1.2. Definition of complete response assessed at 16-20 weeks

Complete response is defined by the presence of **all of the following criteria**:

(1) Satisfactorily passed first (11-13 week) clinical assessment with no evidence of tumour progression. There is no requirement to repeat the MRI for this second assessment.

(2) Using white light endoscopy with phosphate enema (or comparable) bowel preparation, there is no evidence of mucosal tumour, mucosal ulceration or submucosal swelling. **Only a flat, white scar remains with or without telangiectasia.**

(3) There is no palpable tumour upon digital rectal examination.

Where the STAR-TREC criteria for clinical complete response are satisfied, then a patient may be followed by the watchful waiting protocol and TEM surgery is avoided.

9.1.3. Definition of clinical satisfactory but incomplete response assessed at 16-20 weeks

Clinical satisfactory, yet incomplete response is defined using the following criteria:

(1) Satisfactorily passed first (11-13 week) clinical assessment with no evidence of tumour progression. There is no requirement to repeat the MRI for the second assessment.

(2) Using white light endoscopy with phosphate enema (or comparable) bowel preparation **any one** of the following are encountered:

   a. Residual mucosal irregularity
   b. Residual flat ulcer
   c. Submucosal irregularity or swelling

In this situation the presence of persisting tumour cells cannot be excluded. Patients should undergo TEM surgery (or equivalent technique) within 4 weeks of the second clinical assessment. NB. No biopsy is required at this stage and TEM is recommended in all cases.

Clinical response that does not satisfy criteria for CR will have the tumour site locally excised using a suitable single port transanal endoscopic platform such as TEM or equivalent technique. The tumour site is removed by sharp dissection under direct vision, aiming for a 1cm margin of normal mucosal tissue. Both tumour and underlying muscular wall of the rectum are removed en-bloc. A thin layer of perirectal fat is also removed. The mesorectum is not extensively dissected. The specimen is then pinned out in the operating room according to histopathology guidelines. The histopathological features of the resection specimen as detailed below will then determine if the patient will proceed into the trial clinical follow-up schedule or require conversion to radical TME surgery.

Patients undergoing organ preserving treatment should complete all treatment, including TEM surgery if required, within a 20 week timeframe from the start of (chemo)radiotherapy. Cancer regrowth following complete response or recurrence following TEM should prompt TME surgery. TEM surgery beyond 20 weeks is not recommended in these situations. If the treating clinician considers necessary to perform TEM surgery beyond 20 weeks due to exceptional circumstances, the proposed actions should be discussed and approved in advance by the study Chief Investigator, contacting the UK Coordinating Centre in the first instance.

9.2. Histological Evaluation of TME Primary Resection Specimens

Pathological evaluation of the TME resection specimen will be conducted according to standard international guidelines and will include standardised workup as well as standardised reporting. Key features in the reporting of rectal carcinoma include investigation of depth of tumour invasion and the presence of lymph node involvement. Using these parameters, TNM classification can be assessed. Tumour evaluation will be conducted according to standard international guidelines using the 8th edition of the tumour/node/metastasis (TNM) classification and staging system of malignant tumours,(86, 87) with modifications. The term Mx will be used to refer to patients with indeterminate or insufficient evidence of metastasis.

In addition, an evaluation of the involvement of circumferential resection margins (CRM) (88), quality of surgery by photo (53-55) and tumour regression must be done. A CRM of 1 mm or less is considered involved. The exact measurements to the CRM should be given, and, in cases of lymph nodes or tumour deposits being closer to the CRM than the mass of the primary tumour, two separate CRMs should be measured (one of the closest margin and the other one from the primary tumour mass). The glass slides will be sent for scanning along with the specimen photographs to the national **STAR-TREC** central histopathology laboratory to facilitate central review of these features.

9.2.1. Quality of resection evaluation

The quality of resection is evaluated at two different levels for APEs (mesorectum as well as anal canal) and at one level for anterior resections or Hartmann's (mesorectum).

For details about the different scores, see the **STAR-TREC** Histopathology Guidelines.

9.2.2. Tumour regression score following TME

For patients who convert from organ preservation to standard TME surgery, tumour regression is scored using a four-tiered system: minimal/no regression, moderate regression, single cells/scattered small groups of residual cancer cells and complete pathological response. Complete pathological response is only used after standardised workup of the specimen which includes blocking of the whole tumour area and cutting three levels of each block (cutting interval of 250 µm).

9.3. Histological Evaluation of TEM Specimens

Histopathological assessment of high-risk features in TEM specimens will be key to the **STAR-TREC** study. Patients who exhibit high-risk features following SCRT or CRT will be strongly recommended for conversion to radical surgery. A separate Histopathology Guidelines Document out with this protocol provides further details on the histopathology assessment within **STAR-TREC**.

9.3.1. High risk features

Within the **STAR-TREC** study, the high-risk features which have been selected as indicators for consideration of conversion to radical surgery are:

a) Margin involved by tumour (≤1mm tumour clearance constitutes an involved margin)

b) Tumour stage ≥ypT2

c) N+ (occasionally a lymph node will be retrieved with the local excision specimen)

9.3.2. Tumour regression score for TEM resections

Tumour regression is scored using a four-tiered system: minimal/no regression, moderate regression single cells/scattered small groups of residual cancer cells and complete pathological response. Complete pathological response is only used after standardised workup of the specimen which includes blocking of the whole tumour area and cutting three levels of each block (cutting interval of 250 µm).

9.4. Conversion from Organ Saving to TME Surgery

The presence of one high-risk feature should prompt strong consideration of conversion to TME surgery. Presence of two or more high-risk feature should prompt very strong consideration of conversion to TME surgery. For patients who undergo conversion, TME surgery will be performed in a timely fashion, generally within 8-16 weeks of the initial transanal surgical procedure, once post-surgical inflammation has had time to settle. Patients who experience wound dehiscence following TEM are likely to have a degree of mesorectal inflammation. This can lead to adherence of the mesorectal fascia to adjacent structures close to the TEM site. Allowing extra time for this inflammation to resolve combined with sharp

dissection of the mesorectal fascia at the level of the TEM will help overcome intraoperative difficulty. Extra care should be taken when handling the specimen to avoid excessive traction forces that may fracture the specimen following TEM, especially in cases where the bowel wall either was not sutured or the sutures dehisced.

Previous local excision is likely to distort the mesorectum and this may make interpretation of resection margins difficult, particularly in areas where the mesorectum is thin, typically over the levator muscles and anteriorly adjacent to the prostate and seminal vesicles in the male and vagina in females. This may lead to increased use of extra-levator abdomino-perineal resection in preference to restorative anterior resection.

9.5. Schedule of Assessments

The minimal set of assessments for **STAR-TREC** patients is detailed in this section. Each centre can perform additional visits, endoscopies or imaging as per national protocol or patient/doctors preference.

Every effort should be made to schedule follow-up assessments as specified in the protocol. Annual follow-up will continue until 36 months from start of (chemo)radiotherapy or date of initial surgery. Further follow-up beyond 36 months will be according to national guidelines. For UK patients, overall survival data up to 60 months will be obtained via NHS Digital.

9.5.1. Baseline assessments

Written informed consent is required prior to performing any trial-specific procedure. Assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated time frame prior to registration.

A) Within 42 days prior to trial entry

- Medical History
  Including details of current colorectal cancer, previous and current medical conditions and previous treatments received.
- ECOG performance status
- Physical examination
- Digital rectal examination

For patients choosing organ preservation only

- Colonoscopy with biopsy
- Histopathology assessment of the biopsy specimen to confirm presence of rectal adenocarcinoma

  This will include preparation of standard formalin-fixed paraffin embedded tissue blocks and Haematoxilin and Eosin (H&E) matched slides.
- High resolution MRI pelvis

  Recommended within 42 days prior to trial entry, but a maximum of 63 days prior to trial entry is permitted.
- Optional ERUS

  High quality ERUS will be used where the patient is unable to tolerate MRI. Optional ERUS may also be used to supplement MRI in centres where this is available.

  Recommended within 42 days, maximum of 63 days prior to trial entry
- CT-Thorax-abdomen-pelvis with contrast

  Recommended within 42 days prior to trial entry, but a maximum of 63 days prior to trial entry is permitted.
- Radiotherapy planning

  For patients choosing organ preservation only.
- Collection of peripheral blood samples

  For organ preservation patients consenting to the translational sub-study only (see section 9.7)
- Completion of the baseline HRQoL booklet (see section 9.8)

<u>B) Within 7 days prior to trial entry</u>

- Height and weight

  For patients allocated CRT only. These measurements may also be taken at any time after randomisation and prior to starting chemoradiotherapy.
- Pregnancy test

  Only for females of child-bearing potential choosing organ preservation. Both urine hCG and serum βhCG are allowed
- Concomitant medication check
- Eligibility should be confirmed by the MDT prior to trial entry

9.5.2. Clinical assessments and follow-up for the standard TME surgery arm

- Pre-surgical assessment as per local practice
- TME surgery:

  Permitted techniques include:
  - Reconstructive
    - Low anterior resection with stoma formation (weeks 1-6)
    - Stoma reversal (>week 20)
  - Non-reconstructive
    - Abdominoperineal excision or low Hartman's procedure (weeks 1-6)
- AEs / Serious Adverse Events (SAEs) reporting

  Assessment of surgical morbidity will be recorded post-operatively until 30 days after each surgical procedure.

  AEs / SAEs will be reported according to the CTCAE v4.03 within 30 days of each surgical procedure. Surgical SAEs should also be classified using the Clavien-Dindo system (Appendix 4).
- Histopathology of the surgical resection specimen (please refer to histopathology guidelines)
- Follow-up visits:
  - Physical examination:
    - At 6, 12, 24, 30 and 36 months
  - CT scan thorax abdomen pelvis
    - At 24 and 36 months only
    - CT scan thorax abdomen is permitted if complemented with high resolution MRI pelvis
  - Colonoscopy
    - Once within 3 years of initial surgery as per national guidelines
  - Survival status
- Completion of the HRQoL booklet
  - At 3, 12, 24 and 36 months (see section 9.8)

9.5.3. Clinical assessments and follow up for the organ preservation arms

- CRT arm only: Blood tests

  To be performed prior to starting treatment and weekly during the duration of chemo-radiotherapy, including:

  - Full blood count
    - Platelets
    - Absolute neutrophil count
    - White blood cell count
  - Biochemistry
    - Alanine transaminase (ALT) or Aspartate transaminase (AST),
    - Bilirubin
    - Creatinine clearance

- Toxicity assessment

  AEs/SAEs will be reported according to the CTCAE v4.03 during (chemo)radiotherapy treatment and until 30 days after the last dose of trial treatment.

  Assessment of surgical morbidity will be recorded post-operatively until 30 days after each surgical procedure. AEs/SAEs will be reported according to the CTCAE v4.03 within 30 days of each surgical procedure. Surgical SAEs should also be classified using the Clavien-Dindo system (Appendix 4).

- Response assessment at week 11-13 (see section 9.1.1)
  - High resolution MRI pelvis
  - Physical examination
  - Digital rectal examination
  - Rectal endoscopy (colonoscopy, flexible sigmoidoscopy, proctoscopy or equivalent technique)

  Radiotherapy response will determine subsequent steps. Responding patients will be assessed again at week 16-20. Patients showing poor response will be recommended to crossover to TME surgery.

- Response assessment at week 16-20 (see section 9.1.2)
  - Physical examination
  - Digital rectal examination

- Rectal endoscopy (colonoscopy, flexible sigmoidoscopy, proctoscopy or equivalent technique)

Radiotherapy response will determine subsequent treatment (watch and wait, TEM surgery or conversion to TME surgery, see section 3.1 for further details).

Patients undergoing TME surgery after (chemo)radiation therapy will be followed up according to the specific TME schedule.

- Collection of peripheral blood samples

  For patients consenting to the translational sub-study only (see section 9.7)
  - At week 16-20, and at 6, 12, 18 and 24 months.
- Completion of the baseline HRQoL booklet (see section 9.8)
  - At 3, 12, 24 and 36 months
- Follow-up visits:
  - Physical examination:
    - At 6, 9, 12, 18, 24, 30 and 36 months
  - Digital rectal examination:
    - At 6, 9, 12, 18, 24, 30 and 36 months
  - Colonoscopy
    - Once within 3 years of initial surgery as per national guidelines.
  - Rectal endoscopy
    - At 6, 9, 12, 18, 24, 30 and 36 months

      Colonoscopy, flexible sigmoidoscopy, proctoscopy or equivalent technique are allowed
  - High resolution MRI pelvis
    - At 6, 9, 12, 18, 24, 30 and 36 months
  - CT scan thorax abdomen pelvis **OR** CT scan thorax
    - At 24 and 36 months only
  - Survival status

9.6. Patient Withdrawal

Patients may withdraw at any time during the **STAR-TREC** trial if they choose not to continue or if their clinical team feel that continued participation in the trial is inappropriate.

In the event of a patient's decision to withdraw from the trial, the Investigator must ascertain from which aspects of the trial the patient wishes to withdraw, and record the details on the Withdrawal Form and in the medical notes.

The types of withdrawal in **STAR-TREC** are:

- Level 1: Withdrawal from trial-specific treatment:

  The patient will not complete treatment as per the **STAR-TREC** protocol. Follow-up according to the protocol will still be requested.

- Level 2: Withdrawal from trial-specific follow-up:

  The patient has had trial treatment but does not wish to be followed up according to the protocol. The patient will be followed up according to standard practice. (i.e. the patient does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinical visits). It must be confirmed that the patient has agreed that follow-up data collected at standard clinic visits may be used in the final analysis.

  - UK patients should be asked if data held by central registries at The Health and Social Care Information Centre can still be collected for the study.

- Level 3: Complete withdrawal:

  The patient is not willing to be followed up in any way for the purposes of the trial at any further visits and for no further data to be collected, i.e. only data collected prior to the withdrawal of consent can be used in the final analysis.

Only Level 3 is regarded as withdrawal of patient consent.

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data.

All information and tissue samples collected up until the point of retraction will be retained and analysed.

9.7. Blood and Tissue Sample Collection

Patients recruited to the **STAR-TREC** trial (both phase II and phase III) are expected to give consent for the collection of tissue resection specimens and Haematoxilin and Eosin (H&E) matched slides from their diagnostic biopsy and surgery.

Patients recruited to the organ preservation arms during phase III will also be asked to consent to the collection of optional peripheral blood samples for translational research.

Separate Translational Study Guidelines and Histopathology Guidelines are available for participating centres.

Each participating country has a dedicated **STAR-TREC** central histopathological laboratory. Tissue samples will be stored locally at each of these laboratories prior to being centrally collated at the **STAR-TREC** central laboratory at St James's University Hospital, Leeds, UK.

Samples will be stored in accordance with the relevant institutions´ established standard operating procedures and in accordance with GCP.

The International TMG will retain custodianship of patient samples during the course of the study; thereafter custodianship will rest with the Cancer Research UK Clinical Trials Unit (CRCTU) Director who will act on behalf of the Coordinating Sponsor. Full clinico-pathological data for each sample will be stored in the trial database together with a sample identifier.

9.7.1. Blood samples

Provided the patient consented to their blood being taken for research, all centres will collect six sets of blood samples per organ preservation patient recruited during phase III at the following time points:

(a) at baseline

(b) during response assessment at 16-20 weeks

(c) after 6 months (i.e. 24-30 weeks) following completion of initial treatment

(d) 3 times during follow up at 12, 18 and 24 months from the start of (chemo)radiotherapy.

At each time-point a sample of 50ml peripheral blood will be collected and sent by post or courier to the processing laboratory. For patients recruited in the UK, the UK Coordinating Centre will provide blood collection tubes and cover the samples shipping costs.

Blood samples should be labelled with the **STAR-TREC** trial number but no other patient identifiers and shipped to the central translational laboratory allocated to that participating country. A separate translational study guidelines document will describe these methods in more detail.

These blood samples will be used in translational research projects investigating blood circulating tumour DNA (ctDNA) genomic markers associated with persistence of tumour tissue following organ preserving treatment. The utility of ctDNA for determination of partial versus complete response, and the decision to proceed to perform local transanal excision will be assessed. The use of serial ctDNA measurement for early identification of failure of organ preservation treatment, and the decision to convert to standard radical surgery will also be evaluated. Completion of these objectives is subject to securing additional funding.

Patients will also be invited to consent for any remaining samples being used for other ethically approved, yet unplanned research projects.

9.7.2. Haematoxylin and Eosin slides

Following local reporting, either the original glass slides or a duplicate set of H&E slides of the diagnostic pre-operative biopsy and any resected tumour (by both TEM and TME surgery) should be sent to the national **STAR-TREC** central histopathology laboratory along with a copy of the pseudo-anonymised pathology report clearly labelled with the participant's **STAR-TREC** trial number. Slides will be labelled with the local histology number and **STAR-TREC** trial number but no other patient identifiers.

Slides sent to the national histopathology laboratories will then be logged and scanned to provide a permanent record of the pathology prior to returning to the originating hospital in the same state in which they were taken. This will facilitate central review to assess the quality of pathology and surgery within the trial and confirm the histopathological response to (chemo)radiation for patients in the organ preservation arms. The anonymised slides linked to the trial number will be hosted at www.virtualpathology.leeds.ac.uk.

9.7.3. Paraffin-embedded tissue blocks

Routine formalin fixed paraffin-embedded (FFPE) blocks will be collected for all phase II and phase III patients recruited to the standard surgery and organ preservation arms:

- From the diagnostic biopsy (x1 containing tumour)
- From the associated tumour resection (x2 containing tumour plus 1x normal mucosa if available)

Scanned H&E sections will be used to exclude samples with insufficient tumour content. Sections will be cut from tissue blocks with sufficient material for molecular analyses.

1. Diagnostic tissue biopsies will be collected and stored for all subjects. These will be screened for driver mutations to inform the ctDNA work or used to study candidate biomarkers for prediction of response to radiotherapy. Ideally 4 pre-treatment biopsies will be retained in each case.
2. A FFPE tumour block and a normal mucosal block from the primary tumour site will be requested for patients undergoing either TEM or TME surgery.

Tissue should be labelled with the local histology number and **STAR-TREC** trial number but no other patient identifiers and sent to their national **STAR-TREC** central histopathology laboratory including the pseudo-anonymised associated pathology reports clearly labelled with the participant's **STAR-TREC** trial number.

At the end of the **STAR-TREC** study, all remaining tissue samples will be stored in a Human Tissue Authority (HTA)-licenced establishment.

9.7.4. Photographs of specimens

Photographs of the specimens will be collected for central review of the quality of surgery and sections of the histology. All images must include a metric scale (i.e. a ruler). All photographs should be sent electronically to the UK Coordinating Centre. Further details are provided in the pathology guidelines.

9.8. Evaluation of Patient-reported Outcomes Including Symptomatic Toxicity and Health-related Quality of Life

Cancer treatments may produce adverse effects that diminish patient HRQoL, even when tumour regression or extended survival is achieved. The acceptance of any new treatment regimen may be critically dependent on HRQoL consequences. Thus a detailed assessment of symptoms and HRQoL consequences for each of the treatment strategies evaluated is an important aspect of this trial. Inclusion of patient-reported outcomes (validated questionnaires) is the standard for assessment of patient's symptomatic toxicity and overall patient experience in cancer clinical trials.(89)

In order to assess patient-reported symptomatic toxicity, health economics and HRQoL, all recruited patients will be asked to complete the following questionnaires, written in their country's language, at baseline (after informed consent is obtained but before trial entry) and 3, 12, 24 and 36 months after the start of trial-specific treatment:

- EORTC QLQ-C30
- EORTC QLQ-CR29
- EuroQoL EQ-5D-3L
- ICIQ-MLUTS
- ICIQ-FLUTS
- LARS Score

Further details on the HRQoL questionnaires are provided in section 2.2.

Sites will be provided with a supply of HRQoL booklets at site initiation.

Prior to completing the baseline HRQoL booklet, a member of the Research Team should discuss the questionnaires with the patient and answer any questions they may have. Subsequent HRQoL booklets may be given to the patient during clinic appointments or sent on the post. The Research Team should return the completed booklets to the UK Coordinating Centre, which will be responsible for their data entry.

10. Adverse Event Reporting

10.1. Reporting Requirements

The collection and reporting of AEs will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 5. The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the participant with reference to the SmPC for the IMP used in this trial. This should be documented in the source data.

10.2. Adverse Events

AEs are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental treatment. All AEs reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Abnormal results for laboratory tests other than those requested on the CRFs should only be reported as an AE if they fulfil any of the Serious Adverse Event (SAE) criteria or are the reason for treatment discontinuation or dose modifications.

NOTE: In this study, the following events are not reported as an AE or SAE:

- planned surgery (e.g. stoma removal)
- planned hospitalisation (e.g. for administering chemotherapy)
- locoregional or distant cancer recurrences
- death due to progression of disease

10.3. Serious Adverse Events

Investigators will report AEs that meet the definition of an SAE (as defined in Appendix 5) on an SAE Form as described in section 10.5.2.

10.3.1. Monitoring pregnancies for potential Serious Adverse Events

There is an identified risk of congenital anomalies or birth defects in the offspring of participants receiving chemoradiotherapy. The outcome of pregnancies of participants recruited to the CRT arm will therefore be monitored in order to provide SAE data on congenital anomalies or birth defects.

If a patient allocated CRT becomes pregnant during the course of the trial, trial treatment should be discontinued immediately.

In the event that a participant allocated CRT or their partner becomes pregnant during the SAE reporting period, a pregnancy notification form will be completed (providing the participant's details) and returned to the UK Coordinating Centre within 1 working day.

- If it is the participant who is pregnant, outcome data will be provided on a follow-up pregnancy notification form.
- Where the participant's partner is pregnant, consent must first be obtained and the participant should be given a pregnancy release of medical information form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the pregnancy release of medical information form.

Once consent has been obtained, details of the outcome of the pregnancy should be provided on a follow-up pregnancy notification form even if the patient has discontinued trial treatment.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have caused an event fulfilling the definition of a SAE. Congenital abnormalities, birth defects, neonatal death, spontaneous miscarriages, and induced abortion should be reported on an SAE Form.

10.4. Reporting Period

Details of all AEs and SAEs (except those listed above in section 10.2) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last trial treatment.

10.5. Reporting Procedure – At Site

10.5.1. Adverse Events

For all patients:

AEs should be reported on the **STAR-TREC** CRF and, if appropriate, on an SAE Form.

AEs should be coded according to CTCAE v 4.03 (Appendix 2), with the exception of perineal skin reactions due to radiotherapy, which should be graded using the modified RTOG/EORTC Late Radiation Morbidity Scoring system (Appendix 3).

Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the appropriate CRF using a scale of (1) mild, (2) moderate,(3) severe or (4) life-threatening.

10.5.2. Serious Adverse Events

AEs defined as serious and which require reporting as an SAE will be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.03 (Appendix 2, also available online on the National Cancer Institute (NCI) website at the time of writing: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Surgical complications reported on the SAE form will also be graded according to the Clavien-Dindo system (Appendix 4).(90, 91)

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the UK Coordinating Centre at the University of Birmingham, as soon as possible and no later than 24 hours after first becoming aware of the event:

ALL SAEs must be recorded on the SAE form and faxed

to the UK Coordinating Centre on +44 (0) 121 414 2230 or +44 (0) 121 414 7989

within 24 hours of the research staff becoming aware of the event.

(Alternatively, with prior agreement,

SAEs can be emailed to reg@trials.bham.ac.uk)

On receipt, the UK Coordinating Centre will allocate each SAE a unique reference number. This number will be either transcribed onto the SAE Fax Cover Sheet and faxed back to the site; or emailed to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, please contact the UK Coordinating Centre. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet (or acknowledgment email) completed by the UK Coordinating Centre should be filed with the SAE Form in the Investigator Site File.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and outcome assessments. The form should then be returned to the UK Coordinating Centre and a copy kept in the Site File.

Investigators should also report SAEs to their own hospital in accordance with local practice.

10.5.3. Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

10.6. Reporting Procedure – UK Coordinating Centre

On receipt, the UK Coordinating Centre will allocate each SAE a unique reference number. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the TMF.

On receipt of an SAE Form at the UK Coordinating Centre, a Clinical Coordinator will determine seriousness and causality independently. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial treatment will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator, on behalf of the Coordinating Sponsor, will assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.7. Reporting to the Competent Authorities and Research Ethics Committees

10.7.1. Suspected Unexpected Serious Adverse Reactions

The UK Coordinating Centre will notify the NCCs of all SUSARs. SUSARs will be reported to the Competent Authority and research ethics committee in each country by the relevant NCC (the UK Coordinating Centre will undertake this responsibility in the UK). If the event is a fatal or life threatening SUSAR an initial report will be made within 7 days and followed up by a detailed report within 8 days. All other events categorised as SUSARs will be reported within 15 days.

A copy is also sent to the University of Birmingham Research Governance Team (researchgovernance@contacts.bham.ac.uk, subject line should read: SUSAR RG_15-011) at the time of sending the SUSAR report.

10.7.2. Serious Adverse Reactions

The UK Coordinating Centre will report details of all SARs (including SUSARs) in the form of a Development Safety Update Report (DSUR). The DSUR will be sent to each NCC for submission to the Competent Authority and research ethics committee in each country (the UK Coordinating Centre will undertake this responsibility in the UK).

A copy is also sent to the University of Birmingham Research Governance Team at the time of sending the DSUR.

10.7.3. Adverse Events

Details of all AEs will be reported to the Competent Authorities on request.

10.7.4. Other safety issues identified during the course of the trial

The Competent Authorities and Research Ethics Committees will be notified immediately if a significant safety issue is identified during the course of the trial. The UK Coordinating Centre (on behalf of the Coordinating Sponsor) will notify the NCC for each member state concerned and they will be responsible for notifying their regulatory bodies.

The University of Birmingham Research Governance Team will also be informed at the time that the UK research ethics committee and the Medicines and Healthcare Regulatory Agency (MHRA, the UK Competent Authority), is informed.

10.8. Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

10.9. Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

11. Data Handling and Record Keeping

11.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Source data is kept as part of the participants' medical notes generated and maintained at site. For the purpose of the **STAR-TREC** trial the HRQoL booklets retained by the UK Coordinating Centre are also regarded as source data. In addition, for the **STAR-TREC** trial MRIs are performed; their source data will be kept in electronic radiological databases as used at each of the participating sites.

11.2. Data Collection

It will be the responsibility of the Investigator to ensure the accuracy of all data entered in the CRFs. The **STAR-TREC** Site Signature and Delegation Log will identify all those personnel with responsibilities for data collection.

Data reported on each CRF will be consistent with the source data and any discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed. Staff delegated to complete CRFs will be trained to adhere to GCP and also the requirements of data capture as per trial guidelines.

STAR-TREC will use an electronic remote data capture (eRDC) system to capture the CRF data. Access to the eRDC system will be granted to individuals by the UK Coordinating Centre.

https://www.cancertrials.bham.ac.uk

The Investigator and site staff will ensure all data from subject visits are promptly entered into the eRDC in accordance with the trial specific User Manual and CRF Completion Guidelines. The CRF must be completed by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log). The exceptions to this are the Trial Entry Form, SAE Form and Deviation Form which can be completed by an authorised member of the site research team but must be co-signed by the Investigator.

For the purposes of this trial, SAE Forms and HRQoL booklets will be captured on paper and entered onto the eRDC system by the UK Coordinating Centre. The original HRQoL booklets will be returned to the UK Coordinating Centre and will be regarded as source data.

Paper CRFs will also be available as a backup. When using paper CRFs, these must be completed, signed/dated by the Investigator or an authorised member of the site research team (as delegated on the **STAR-TREC** Site Signature and Delegation Log) and returned to the UK Coordinating Centre for data entry onto the trial database

Entries on the CRF should be made in ballpoint pen, preferably in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

The UK Coordinating Centre may amend CRFs, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

11.3. Archiving

All records created by following trial procedures and all documents listed in guidance relating to the conduct of the trial must be retained and archived.

Archiving will be authorised by the UK Coordinating Centre on behalf of the Coordinating Sponsor following submission of the end of trial report.

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy File, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years after the end of the trial.

No documents will be destroyed without prior approval from the CRCTU Document Storage Manager.

12. Quality control and quality assurance

The trial is being conducted under the auspices of the CRCTU according to the current guidelines for GCP. Participating sites will be monitored to confirm compliance with the protocol, and the protection of patients' rights as detailed in the Declaration of Helsinki.

12.1. Site Set-up and Initiation

All sites will be required to sign a site agreement prior to participation. All participating Principal Investigators will be asked to sign the necessary agreements, registration forms and supply a current CV and evidence of GCP training to their NCC. All members of the site research team will also be required to sign a Site Signature and Delegation Log which should be returned to the UK Coordinating Centre. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed GCP training. Key members of the site

research team will be required to attend either a meeting or teleconference call covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The relevant NCC and the UK Coordinating Centre must be informed immediately of any change in the site research team.

12.2. Monitoring

12.2.1. On-site Monitoring

On-site monitoring will be carried out as required following a risk assessment and as documented in the Quality Management Plan for each participating country.

Any monitoring activities will be reported to the UK Coordinating Centre and any issues noted will be followed up to resolution.

Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive toxicity and/or number of participant withdrawals or deviations. If a monitoring visit is required the relevant NCC will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the **STAR-TREC** trial staff access to source documents as requested.

12.2.2. Central Monitoring

STAR-TREC will also be centrally monitored. The relevant NCC will be in regular contact with the site research teams to check on progress and address any queries that they may have. The UK Coordinating Centre will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Where allowed by national legislation, sites will send the UK Coordinating Centre copies of signed Informed Consent Forms and other documentation for in-house review for all participants who have provided consent.

12.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. NCCs and sites are also requested to notify the UK Coordinating Centre of any Competent Authority inspections.

12.4. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulation 2004 and its amendments, the Coordinating Sponsor is responsible for notifying the MHRA in writing of any serious breach of the conditions and principles of GCP in connection with that trial, or the protocol relating to that trial, within 7 days of becoming aware of that breach.

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 participants of the trial; or

(b) the scientific value of the trial.

For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree:

(a) the conditions and principles of GCP in connection with the trial; or

(b) the protocol relating to the trial, as amended from time to time, within 7 days of becoming aware of that breach.

Sites are therefore requested to notify their NCC of any suspected trial-related serious breach of GCP and/or the trial protocol. The NCC will notify the UK Coordinating Centre who will investigate the incident and where necessary implement a corrective and/or preventive action plan. Where the UK Coordinating Centre is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the UK Coordinating Centre or NCC in providing additional information. Where a breach is confirmed, the UK Coordinating Centre will report the breach to the UK Competent Authority, research ethics committee, and NCCs who will be responsible for reporting the incident to their Competent Authority and research ethics committee in accordance with country specific requirements. A copy of the Serious Breach report will also be sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the UK research ethics committee.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and /or poor recruitment. Any major problems identified during monitoring may be reported to the TMG, the research ethics committee and relevant regulatory bodies.

13. End of Trial Definition

The end of trial will be 12 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input.

The UK Coordinating Centre will notify the MHRA and UK research ethics committee that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the UK Coordinating Centre will inform the MHRA and UK research ethics committee within 15 days of the end of trial. The UK Coordinating Centre will provide them with a summary of the clinical trial report within 12 months of the end of trial. The UK Coordinating Centre will notify the NCCs that the trial has ended and it will be their responsibility to notify the Competent Authority and research ethics committee within their country.

A copy of the end of trial notification as well as the summary report will be sent to the University of Birmingham Research Governance Team at the time these are submitted to the Competent Authorities and research ethics committees.

14. Statistical Considerations

Statistical analysis will be performed by the UK Coordinating Centre.

14.1. Definition of Outcome Measures

14.1.1. Primary outcome measures

See section 2.2.1

14.1.2. Secondary outcome measures/exploratory endpoints

See section 2.2.2.

14.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) for **STAR-TREC** will provide a detailed description of the planned analyses for the trial. A brief outline of these analyses is provided below.

14.2.1. Analysis of outcome measures for phase II

For the **STAR-TREC** phase II feasibility study the primary endpoint is a measure of recruitment rate. Should the target recruitment rates be met then the primary endpoint will have been achieved.

The secondary endpoints encompass international funding, international opening of the trial, and efficacy of the organ preserving treatment. If one international partner procures **STAR-TREC** funding then this endpoint will have been achieved. If one international partner opens the **STAR-TREC** study then this endpoint will have been achieved. For the efficacy endpoint, an experimental arm will need to show >50% organ preservation at 12 months post-randomisation. Organ preservation in this context is defined as not proceeding to TME surgery. The proportion of participants with organ preservation will be calculated for each of the treatment arms separately, not combined over the two experimental arms. For an experimental arm to continue into a phase III study it would need to show >50% organ preservation independently of the other experimental arm.

For the phase II feasibility study no hypothesis tests are planned as the study would be underpowered to identify any differences between the treatment arms. Summary statistics will be calculated as appropriate (means and standard deviations / median and interquartile range for continuous variables, numbers and proportions for categorical variables).

All analyses in **STAR-TREC** phase II will be conducted using the intention to treat principle – where participants are analysed in the treatment group to which they were randomised, regardless of the treatment received. All participants will be used in the analyses. A p-value of <0.05 will be considered statistically significant.

The primary objective of a future phase III study would be to independently compare the two organ preservation treatments. The outcomes for a **STAR-TREC** phase III study will be informed by the feasibility study. A selection of possible outcomes is described in section 2.2. Dichotomous variables (such as response and organ preservation rates) will be compared using chi-squared tests; ordinal variables (such as toxicity grades) will be analysed using Mantel-Haenszel tests; and continuous outcome measures such as quality of life scores will

be analysed using independent t-tests or repeated measures regression techniques. Adverse events will be summarised descriptively by treatment arm, and the number of events and percentage of participants experiencing any adverse event reported.

There are no formal stopping rules. The independent DMC will monitor the rates of acute toxicity, organ preservation and pelvic relapse at regular intervals.

14.2.2. Analysis of outcome measures for phase III

The analytical strategy aims to evaluate whether (a) either organ-saving strategy is superior in terms of achieving organ preservation, requirement for further surgery, treatment related toxicity, health-related quality of life, and other outcomes; (b) either or both organ-saving strategies lead to an acceptable rate of organ preservation of at least 50%. The primary analyses in **STAR-TREC** phase III will be conducted according to the intention to treat principle, where participants are analysed in the treatment group to which they were randomised, regardless of the treatment received.

In a comparison of two active treatments, the goal of the analysis is to identify whether either of them is superior. Because the difference between two active treatments may be relatively small, conventional statistical significance ($p<0.05$) is not an appropriate criterion, because important differences may well not be statistically significant. Moreover, if only significant differences are regarded as establishing the superiority of one of the interventions, the treatment effect is likely to be substantially exaggerated (because significance will only occur where by chance the estimated treatment effect is large). Instead, we propose to use Bayesian methods, which will estimate the probability that each treatment is superior, as well as providing estimates of the treatment effect and its uncertainty. There is no fixed threshold for regarding a treatment as sufficiently likely to be superior that it should be adopted in preference to the alternative, because this is a clinical judgement that will depend on other effects of the intervention and patient characteristics. In the sample size calculations below, we have adopted a criterion of greater than 80% probability of being the best treatment as indicating that a treatment is convincingly better. For all parameters in the Bayesian models, we will use weakly informative priors, that will put low probability on unrealistic values. Where possible, these will be informed by existing evidence. Priors will be specified fully in the statistical analysis plan.

The primary analysis will be the randomised comparison of the two organ-preserving treatments. We will analyse each outcome separately, in the traditional way, but we will also

perform a patient-centred analysis, in which we will analyse the overall outcome for each patient, using a ranked composite outcome of all the possible combinations of death, cancer treatment failure and failure of organ preservation.

Dichotomous outcome measures such as the primary outcome, and need for further surgery, will be analysed using Bayesian logistic regression models, with adjustment for baseline covariates known to be related to outcomes. Health-related quality of life will use hierarchical models to model each patient's trajectory through time, to account for the multiple data points per patient.

The patient-centred ranked composite outcome analysis will classify each patient's overall outcome, based on mortality, organ preservation, treatment-related toxicity, need for surgery and quality of life, into an ordinal scale. The ranking of outcome categories will be determined by consensus among the investigators during the conduct of the trial, and will be reviewed (and potentially modified) by a sample of clinicians and patients. A full description of the outcome will be included in the Statistical Analysis Plan. The ordinal overall outcome measure will be used to compare the randomised groups, using ordinal regression models. The main advantages of this approach are that it is more relevant to patients because it considers patients' overall outcome, and it enables all patients' outcomes to contribute to the analysis (92, 93).

We will conduct an additional exploratory analysis of the timing of organ loss, using 2-part modelling techniques to model the probability of organ loss, and the timing to removal for those patients that do not achieve organ preservation. This will allow us to estimate the difference in timing of organ removal between the arms, for the patients that have this outcome.

For the non-randomised comparison of organ preservation and standard radical surgery, we will compare the toxicity (clinician and patient-reported) and quality of life outcomes for patients who chose radical surgery with those who received organ-preserving treatment in the two randomised arms. We will use regression models to explore the effects of treatment (radical surgery versus organ-preserving treatment) on the outcomes of interest. Because this is a non-randomised comparison, confounding is likely to be an issue, and we will therefore include in the models' baseline factors thought to be associated with outcomes, including age, sex and disease severity, and factors that appear to differ between the groups being compared. Decision regret will be evaluated at 12 and 24 months.

14.2.3. Planned randomisation methodology

See section 6.2.

14.2.4. Planned sub group analyses

Phase II

No subgroup analyses are planned for the feasibility study due to the small number of participants.

Phase III

Subgroup analyses will be performed by i) stratification factors (country and tumour staging); and ii) translational ctDNA results obtained as part of the trial substudy (samples taken at 6 timepoints (baseline, week 16-20 and at 6, 12, 18, and 24 months).

14.2.5. Planned interim analysis

Interim unblinded analyses of efficacy and safety will be provided in strict confidence to the independent data monitoring committee at least annually, or as per a timetable agreed by the committee prior to the commencement of the study.

Analysis and publication of results of phase II patients will be prepared while phase III is ongoing; this will include general results (such as organ preservation and cancer recurrence rates), and HRQoL analyses. These publications will report results of radical surgery vs blinded combined organ preservation arms in order to avoid disclosing results of the phase III primary outcome.

14.2.6. Planned final analyses

For the phase II study, the final efficacy analyses will start once the last patient randomised has completed the 12 month assessment.

For a phase III study with the proportion of patients with successful organ preservation at 30 months from the start day of (chemo)radiotherapy treatment as a primary endpoint, any final analyses will take place once all recruited patients have completed their protocol assessments.

14.2.7. Sample sizes

Phase II

No power calculation is provided for the feasibility as the main objective is to show feasibility of recruitment.

Phase III

We have set the timescale for recruitment to the phase III study at 4 years, which is acceptable to the clinical community, and the sample size achievable within this is expected to be 380 based upon the current rate of recruitment (this includes 80 pat ients from phase II recruited to organ preservation). The target sample size is always a compromise between the desire to maximise statistical power, and the need to provide high-quality evidence to inform patient care as quickly as possible. The expected incidence of the primary outcome is approximately 60%, and we predict that a 10-15% difference between treatment arms would be regarded as clinically important by both patients and the wider clinical community. Smaller differences are unlikely to promote therapy change due to the presence of established geo-regional practices relating to the use of CRT versus SCRT.

Comparison of organ-preserving strategies

A sample size of 380 allowing for an 8% dropout, yields 350 evaluable cases, which would have a probability of around 80%, or higher, of correctly identifying the superior treatment if the true difference is 10%. In all cases, the probability of identifying the wrong treatment as superior is very low (less than 1%). If the organ preservation rate turns out to be higher than anticipated (70% or 80%), the probability of detecting a 10% improvement remains over 85%. For comparative purposes, a traditional significance test-based sample size calculation shows that 334 patients (167 per randomised arm) would have 80% power to obtain a conventionally statistically significant result ($p < 0.05$), with a true incidence of the primary outcome of 50% in one arm and 65% in the other (absolute difference of 15%). For 50% increasing to 60% (absolute difference of 10%), the conventional calculation gives 385 per group: 770 in total.

Sample size	Incidence arm 1 (%)	Incidence arm 2 (%)	Probability of identifying correct treatment as superior	Probability of identifying wrong treatment as superior
350	50	60	0.8540	0.0033
350	50	65	0.9750	0.0002
350	60	70	0.8689	0.0026

Comparison of observed organ preservation rates with minimum standard

To be considered a viable treatment option, organ preserving strategies need to achieve a high rate of organ preservation. Each arm will be compared with a minimum acceptable threshold of 50%, using a Bayesian posterior distribution to quantify the probability, based on the observed data, that the true organ preservation rate is greater than 50%. Using a requirement for 80% probability that the rate exceeds 50% as the criterion for considering a treatment acceptable, a trial arm of 175 patients would have a probability of 0.845 of satisfying this criterion, if the true organ preservation rate is 60%.

Comparison of organ preservation arms with standard radical surgery

For the non-randomised comparison of organ preservation and standard radical surgery, we anticipate that we will have data for at least 120 patients who have been allocated to standard surgery or chosen that treatment.

15. Trial Organisational Structure

15.1. Coordinating Sponsor

The University of Birmingham is the Coordinating Sponsor of the **STAR-TREC** study. In addition, the University of Birmingham (UK Coordinating Centre) will undertake the responsibilities of NCC in the UK.

NCCs are responsible for the conduct of the trial within their own country in accordance with contractually defined delegated duties and in compliance with the applicable regulations.

15.2. National Coordinating Centres

The Coordinating Sponsor has delegated the set-up, management and analysis of the trial to the UK Coordinating Centre. The role of the UK Coordinating Centre is assumed by the CRCTU, University of Birmingham, UK. The trial will be set-up, managed and analysed in the UK in accordance with CRCTU standard policy and procedures.

Each country will appoint a National Coordinating Investigator and an NCC who will take national responsibility for the study and manage the trial in accordance with the trial protocol, and their standard policy and procedures.

Each NCC will be responsible for implementation of appropriate agreements with local participating sites.

15.3. Trial Management Group

The TMG is composed of the Chief Investigator, Co-Investigators, representatives from each NCC and the trial team at the CRCTU (Trial Statistician, Trial Management Team Leader (or deputy), Trial Coordinator, Clinical Trials Monitor) and patient representative(s). The TMG is responsible for the day-to-day running and management of the trial and will meet by teleconference or in person at regular intervals. They will be responsible for the set-up, promotion, on-going management of the trial, the interpretation of the results and preparation and presentation of relevant publications.

15.4. Phase II Joint Trial Steering and Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet at least annually unless there is a specific reason to amend the schedule. During the recruitment phase of the

trial the DMC is scheduled to meet six months after the recruitment of the first participant and annually thereafter.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified.

The phase II DMC will report directly to the Trial Management Group.

The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

15.5. Phase III Trial Steering Committee

The phase III independent Trial Steering Committee will be set up with an independent chairperson to oversee the trial. Membership will be composed of independent clinicians and a statistician. Select members of the TMG will report to this committee. The Trial Steering Committee will meet during the III trial, at least once a year (usually by teleconference), the meetings will usually be arranged to coincide with DMC meetings. The Trial Steering Committee will oversee the conduct of the trial, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the trial to the Coordinating Sponsor.

15.6. Phase III Data Monitoring Committee

Data analyses from the phase III trial will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet at least annually unless there is a specific reason to amend the schedule. During the recruitment phase of the trial the DMC

is scheduled to meet six months after the recruitment of the first phase III participant and annually thereafter.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified.

The phase III DMC will report to the Trial Steering Committee via the Trial Statistician.

The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety.

15.7. Finance

This is an investigator-initiated and investigator-led trial. **STAR-TREC** is an international study, separately funded in each participating country. In the UK, **STAR-TREC** is funded by Cancer Research UK, in the Netherlands by the Dutch Cancer Society and in Denmark by the Danish Cancer Society.

STAR-TREC can offer no financial support to the collaborating hospitals for treatment of patients included in the study. However, **STAR-TREC** should not incur any additional research costs for participating hospitals. In the UK, site payments will be made to cover the additional research costs (patient randomisation, blood collection for translational samples, preparation of tissue blocks for research purposes, packaging of samples for delivery, distribution of HRQoL questionnaires and archiving).

In the UK, **STAR-TREC** is an NIHR portfolio adopted study.

16. Ethical Considerations

The accepted basis for the conduct of clinical trials in humans is founded on the protection of human rights and the dignity of human beings with regard to the application of biology and medicine, and requires compliance with the principles of GCP and detailed guidelines in line with those principles (Directive 2001/20/EC and Directive 2005/28/EC).

GCP is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible (Article 1 (2) of Directive 2001/20/EC).

The NCCs and Investigators shall consider all relevant country specific regulation and guidance with respect to commencing and conducting a clinical trial (Article 4 of Directive 2005/28/EC).

The conduct of the trial shall be based on the following international ethical and statutory sources:

- The **WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects**
- If the region has adopted the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: **Convention on Human Rights and Biomedicine** (CETS No.: 164)
- **Directive 2001/20/EC** of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L21, 01/05/2001 P. 0034 – 0044) and detailed guidance.
- **Directive 2005/28/EC** of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Official Journal L 91, 09/04/2005 P. 0013 – 0019).
- **Regulation (EU) 2016/679** of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- Scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use, as agreed upon by the CHMP and published by the Agency, as well as the other pharmaceutical Community guidelines published by the Commission in the different volumes of the rules governing medicinal products in the European Community (Directive 2005/28/EC (9)).

Appropriate regulatory, ethical and local institution approval must be obtained before patients are recruited into the trial within each country and site. It will be the responsibility of the NCC to obtain country specific approval and (usually) the responsibility of the Principal Investigator to obtain local approval.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local site specific approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

17. Confidentiality and Data Protection

The University of Birmingham is the Data Controller for this trial. Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation (EU) 2016/679 and the UK Data Protection Act 2018 (GDPR). Data will be processed under Article 6 (i) (performance of a task carried out in the public interest) and Article 9 (j) (necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1)). Information about how information is handled can be found in the Cancer Research UK Clinical Trials Units and University of Birmingham's privacy policies (https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/crctu-privacy-notice.aspx).

Participants will always be identified using only their unique trial identification number on correspondence between the relevant NCC and the participating site. For UK participants, the participant's full name, date of birth, hospital number and NHS number (or CHI number in Scotland) will be collected once at the time of trial entry and held at the UK Coordinating Centre to allow tracing through the Cancer Registries, and NHS Digital to assist with long-term follow-up.

For non-UK participants, name or initials, date of birth and hospital number will be collected if national legislation permits. Where national regulations allow, participants will give their consent for forwarding a copy of their signed consent form to the relevant NCC. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the relevant NCC (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries

from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

The NCC will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. the Competent Authority, Coordinating Sponsor). Representatives of the UK Coordinating Centre and Coordinating Sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

18. Insurance and Indemnity

The Coordinating Sponsor will obtain adequate insurance to cover negligent harm arising from the design of the protocol and its liabilities in relation to the trial.

The NCCs are responsible for obtaining insurance to set up and run the **STAR-TREC** trial in their respective countries and for ensuring that sites in their country are adequately covered.

With respect to the conduct of the trial at Site and other clinical care of the patient, in the UK responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company and, as such, it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

19. Publication Policy

Results of this trial will be submitted for publication in peer-reviewed journals.

Meetings will be held after the end of each phase of the trial to allow discussion of the main results among the collaborators prior to publication. The success of **STAR-TREC** depends on the collaboration of a large number of clinicians across several countries. For this reason, all publications arising from this work will be attributed to the '**STAR-TREC** Collaborative Group'.

Publications will conform to the International Committee of Medical Journal Editors (ICMJE) guidelines (December 2015). When manuscripts are submitted, the corresponding author will specify the name of the **STAR-TREC** group, and clearly identify the group members who can take credit and responsibility for the work as authors. The byline will include the **STAR-TREC** name and allow MEDLINE to list the names of individual group members who are authors or who are collaborators. There will be a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators. In this way, all contributors to the **STAR-TREC** study will be recognised.

The results obtained from patients recruited during the phase II part of the trial, including general results such as organ preservation and cancer recurrence rates and Quality of Life analyses, will be submitted for publication while the phase III part of the trial is ongoing. These publications will report blinded results of both organ preservation arms combined versus results of the radical surgery arm, in order to avoid disclosing results of the phase III primary outcome (direct comparison between organ preservation arms).

The TMG must review any secondary publications and presentations prepared by Investigators. Authors must acknowledge that the trial was performed with the support of the funders and the University of Birmingham as the Coordinating Sponsor. Intellectual property rights will be addressed in the agreements between Coordinating Sponsor, NCCs and sites.

The results of the trial will also be published on a clinical trials registry and a lay summary made available on the Cancer Research UK website.

20. Reference List

1. Atkin WS, Cook CF, Cuzick J, Edwards R, Northover JM, Wardle J, et al. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet. 2002;359(9314):1291-300.
2. Group UCCSP. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. BMJ. 2004;329(7458):133.
3. Gollins S, Moran B, Adams R, Cunningham C, Bach S, Myint AS, et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) - Multidisciplinary Management. Colorectal Dis. 2017;19 Suppl 1:37-66.
4. Bentrem DJ, Okabe S, Wong WD, Guillem JG, Weiser MR, Temple LK, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg. 2005;242(4):472-7; discussion 7-9.
5. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007;246(5):693-701.
6. Endreseth BH, Myrvold HE, Romundstad P, Hestvik UE, Bjerkeset T, Wibe A, et al. Transanal excision vs. major surgery for T1 rectal cancer. Diseases of the colon and rectum. 2005;48(7):1380-8.
7. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. The New England journal of medicine. 2001;345(9):638-46.
8. Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: prospective national study. Bmj. 2003;327(7425):1196-201.
9. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(3):817-25.
10. Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Annals of surgery. 2005;242(2):212-23.
11. Wallner C, Lange MM, Bonsing BA, Maas CP, Wallace CN, Dabhoiwala NF, et al. Causes of fecal and urinary incontinence after total mesorectal excision for rectal cancer based on cadaveric surgery: a study from the Cooperative Clinical Investigators of the Dutch total mesorectal excision trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(27):4466-72.
12. Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Holzel D. Quality of life in rectal cancer patients: a four-year prospective study. Annals of surgery. 2003;238(2):203-13.
13. Temple LK, Bacik J, Savatta SG, Gottesman L, Paty PB, Weiser MR, et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. Diseases of the colon and rectum. 2005;48(7):1353-65.
14. Grumann MM, Noack EM, Hoffmann IA, Schlag PM. Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer. Annals of surgery. 2001;233(2):149-56.

15. Wilson TR, Alexander DJ. Clinical and non-clinical factors influencing postoperative health-related quality of life in patients with colorectal cancer. The British journal of surgery. 2008;95(11):1408-15.
16. Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. The British journal of surgery. 2009;96(3):280-90.
17. Cataldo PA, O'Brien S, Osler T. Transanal endoscopic microsurgery: a prospective evaluation of functional results. Diseases of the colon and rectum. 2005;48(7):1366-71.
18. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Annals of surgery. 2007;245(5):726-33.
19. Garcia-Aguilar J, Mellgren A, Sirivongs P, Buie D, Madoff RD, Rothenberger DA. Local excision of rectal cancer without adjuvant therapy: a word of caution. Annals of surgery. 2000;231(3):345-51.
20. Ricciardi R, Madoff RD, Rothenberger DA, Baxter NN. Population-based analyses of lymph node metastases in colorectal cancer. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2006;4(12):1522-7.
21. Greenberg JA, Shibata D, Herndon JE, 2nd, Steele GD, Jr., Mayer R, Bleday R. Local excision of distal rectal cancer: an update of cancer and leukemia group B 8984. Diseases of the colon and rectum. 2008;51(8):1185-91; discussion 91-4.
22. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731-40.
23. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009;373(9666):811-20.
24. Colorectal cancer: diagnosis and management. Clinical guideline [CG131]. National Institute for Health and Care Excellence.; 2011 [Available from: https://www.nice.org.uk/guidance/cg131.
25. Wong RK, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. Cochrane Database Syst Rev. 2007(2):CD002102.
26. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638-46.
27. Dahlberg M, Glimelius B, Påhlman L. Improved survival and reduction in local failure rates after preoperative radiotherapy: evidence for the generalizability of the results of Swedish Rectal Cancer Trial. Ann Surg. 1999;229(4):493-7.
28. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. The British journal of surgery. 2006;93(10):1215-23.
29. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local

recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(31):3827-33.
30. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355(11):1114-23.
31. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006;24(28):4620-5.
32. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. The New England journal of medicine. 2004;351(17):1731-40.
33. Stipa F, Chessin DB, Shia J, Paty PB, Weiser M, Temple LK, et al. A pathologic complete response of rectal cancer to preoperative combined-modality therapy results in improved oncological outcome compared with those who achieve no downstaging on the basis of preoperative endorectal ultrasonography. Ann Surg Oncol. 2006;13(8):1047-53.
34. Valentini V, Coco C, Picciocchi A, Morganti AG, Trodella L, Ciabattoni A, et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys. 2002;53(3):664-74.
35. Marijnen CA, Nagtegaal ID, Klein Kranenbarg E, Hermans J, van de Velde CJ, Leer JW, et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(7):1976-84.
36. Graf W, Dahlberg M, Osman MM, Holmberg L, Pahlman L, Glimelius B. Short-term preoperative radiotherapy results in down-staging of rectal cancer: a study of 1316 patients. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1997;43(2):133-7.
37. Radu C, Berglund A, Pahlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer - a retrospective study. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2008;87(3):343-9.
38. Erlandsson J, Holm T, Pettersson D, Berglund A, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 2017;18(3):336-46.
39. Pettersson D, Cedermark B, Holm T, Radu C, Pahlman L, Glimelius B, et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg. 2010;97(4):580-7.
40. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014;88(4):822-8.
41. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH, Jr., et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Annals of surgery. 2004;240(4):711-7; discussion 7-8.

42. Glynne-Jones R, Wallace M, Livingstone JI, Meyrick-Thomas J. Complete clinical response after preoperative chemoradiation in rectal cancer: is a "wait and see" policy justified? Dis Colon Rectum. 2008;51(1):10-9; discussion 9-20.
43. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018;391(10139):2537-45.
44. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. The lancet oncology. 2010;11(9):835-44.
45. Garcia-Aguilar J, Shi Q, Thomas CR, Jr., Chan E, Cataldo P, Marcet J, et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Annals of surgical oncology. 2012;19(2):384-91.
46. Garcia-Aguilar J, Renfro LA, Chow OS, Shi Q, Carrero XW, Lynn PB, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol. 2015;16(15):1537-46.
47. Appelt AL, Ploen J, Harling H, Jensen FS, Jensen LH, Jorgensen JC, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol. 2015;16(8):919-27.
48. Verseveld M, de Graaf EJ, Verhoef C, van Meerten E, Punt CJ, de Hingh IH, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). Br J Surg. 2015;102(7):853-60.
49. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA. 2014;311(3):263-70.
50. Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg. 2009;96(3):280-90.
51. Rullier E, Rouanet P, Tuech JJ, Valverde A, Lelong B, Rivoire M, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet. 2017;390(10093):469-79.
52. Smart CJ, Korsgen S, Hill J, Speake D, Levy B, Steward M, et al. Multicentre study of short-course radiotherapy and transanal endoscopic microsurgery for early rectal cancer. Br J Surg. 2016;103(8):1069-75.
53. Swellengrebel HA, Marijnen CA, Verwaal VJ, Vincent A, Heuff G, Gerhards MF, et al. Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer. The British journal of surgery. 2011;98(3):418-26.
54. Gornicki A, Richter P, Polkowski W, Szczepkowski M, Pietrzak L, Kepka L, et al. Anorectal and sexual functions after preoperative radiotherapy and full-thickness local excision of rectal cancer. Eur J Surg Oncol. 2014;40(6):723-30.
55. Coco C, Rizzo G, Mattana C, Gambacorta MA, Verbo A, Barbaro B, et al. Transanal endoscopic microsurgery after neoadjuvant radiochemotherapy for locally advanced extraperitoneal rectal cancer: short-term morbidity and functional outcome. Surgical endoscopy. 2013;27(8):2860-7.

56. Rombouts AJM, Al-Najami I, Abbott NL, Appelt A, Baatrup G, Bach S, et al. Can we Save the rectum by watchful waiting or TransAnal microsurgery following (chemo) Radiotherapy versus Total mesorectal excision for early REctal Cancer (STAR-TREC study)?: protocol for a multicentre, randomised feasibility study. BMJ Open. 2017;7(12):e019474.
57. Nijkamp J, Kusters M, Beets-Tan RG, Martijn H, Beets GL, van de Velde CJ, et al. Three-dimensional analysis of recurrence patterns in rectal cancer: the cranial border in hypofractionated preoperative radiotherapy can be lowered. Int J Radiat Oncol Biol Phys. 2011;80(1):103-10.
58. Roels S, Duthoy W, Haustermans K, Penninckx F, Vandecaveye V, Boterberg T, et al. Definition and delineation of the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys. 2006;65(4):1129-42.
59. Leibold T, Shia J, Ruo L, Minsky BD, Akhurst T, Gollub MJ, et al. Prognostic implications of the distribution of lymph node metastases in rectal cancer after neoadjuvant chemoradiotherapy. J Clin Oncol. 2008;26(13):2106-11.
60. Marijnen CA. Organ preservation in rectal cancer: have all questions been answered? Lancet Oncol. 2015;16(1):e13-22.
61. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum. 2010;53(12):1692-8.
62. Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011;29(35):4633-40.
63. Smith FM, Wiland H, Mace A, Pai RK, Kalady MF. Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy. Diseases of the colon and rectum. 2014;57(3):311-5.
64. Kuo LJ, Chiou JF, Tai CJ, Chang CC, Kung CH, Lin SE, et al. Can we predict pathologic complete response before surgery for locally advanced rectal cancer treated with preoperative chemoradiation therapy? International journal of colorectal disease. 2012;27(5):613-21.
65. Perez RO, Habr-Gama A, Pereira GV, Lynn PB, Alves PA, Proscurshim I, et al. Role of biopsies in patients with residual rectal cancer following neoadjuvant chemoradiation after downsizing: can they rule out persisting cancer? Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2012;14(6):714-20.
66. Oh BY, Yun HR, Kim SH, Yun SH, Kim HC, Lee WY, et al. Features of Late Recurrence Following Transanal Local Excision for Early Rectal Cancer. Dis Colon Rectum. 2015;58(11):1041-7.
67. Perez RO, Habr-Gama A, Sao Juliao GP, Proscurshim I, Coelho AQ, Figueiredo MN, et al. Transanal local excision for distal rectal cancer and incomplete response to neoadjuvant chemoradiation - does baseline staging matter? Dis Colon Rectum. 2014;57(11):1253-9.
68. Paty PB, Nash GM, Baron P, Zakowski M, Minsky BD, Blumberg D, et al. Long-term results of local excision for rectal cancer. Ann Surg. 2002;236(4):522-29; discussion 9-30.
69. Sengupta S, Tjandra JJ. Local excision of rectal cancer: what is the evidence? Dis Colon Rectum. 2001;44(9):1345-61.

70. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol. 2009;35(12):1280-5.
71. Bikhchandani J, Ong GK, Dozois EJ, Mathis KL. Outcomes of salvage surgery for cure in patients with locally recurrent disease after local excision of rectal cancer. Dis Colon Rectum. 2015;58(3):283-7.
72. Alberts SR, Townley PM, Goldberg RM, Cha SS, Sargent DJ, Moore DF, et al. Gemcitabine and oxaliplatin for metastatic pancreatic adenocarcinoma: a North Central Cancer Treatment Group phase II study. Ann Oncol. 2003;14(4):580-5.
73. Morino M, Risio M, Bach S, Beets-Tan R, Bujko K, Panis Y, et al. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. Surg Endosc. 2015;29(4):755-73.
74. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet. 1996;348(9034):1049-54.
75. Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012;13(6):579-88.
76. O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol. 2014;32(18):1927-34.
77. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
78. Gujral S, Conroy T, Fleissner C, Sezer O, King PM, Avery KN, et al. Assessing quality of life in patients with colorectal cancer: an update of the EORTC quality of life questionnaire. Eur J Cancer. 2007;43(10):1564-73.
79. Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer. 2009;45(17):3017-26.
80. 2018 ERF. EQ-5D-3L User Guide. 2018.
81. Donovan JL, Peters TJ, Abrams P, Brookes ST, de aa Rosette JJ, Schafer W. Scoring the short form ICSmaleSF questionnaire. International Continence Society. J Urol. 164. United States2000. p. 1948-55.
82. Brookes ST, Donovan JL, Wright M, Jackson S, Abrams P. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. Am J Obstet Gynecol. 2004;191(1):73-82.
83. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg. 2012;255(5):922-8.
84. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, Tiret E, Xynos E, Beets-Tan RGH, et al. Definition of the Rectum: An International, Expert-based Delphi Consensus. Ann Surg. 2019.
85. Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours, 8th edition.: Oxford: John Wiley & Sons, Inc.; 2016.

86. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg. 2012;99(9):1211-8.
87. Bujko K, Richter P, Smith FM, Polkowski W, Szczepkowski M, Rutkowski A, et al. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: a prospective multicentre study. Radiother Oncol. 2013;106(2):198-205.
88. Borschitz T, Wachtlin D, Möhler M, Schmidberger H, Junginger T. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol. 2008;15(3):712-20.
89. US Food Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims [Washington, D.C.]: Federal Register; 2009 [65132].
90. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
91. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.
92. Armstrong PW, Westerhout CM, Van de Werf F, Califf RM, Welsh RC, Wilcox RG, et al. Refining clinical trial composite outcomes: an application to the Assessment of the Safety and Efficacy of a New Thrombolytic-3 (ASSENT-3) trial. Am Heart J. 2011;161(5):848-54.
93. Evans SR, Follmann D. Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes: A Step toward Pragmatism in Benefit:risk Evaluation. Stat Biopharm Res. 2016;8(4):386-93.
94. Brierley JD, Gospodarowicz, K M, Wittekind C. TNM Classification of Malignant Tumours , 8th edition.: Oxford : John Wiley & Sons, Inc . 2016.
95. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv22-iv40.

Appendix 1 –Tumour Staging – TNM Classification 8th Edition

Tumour evaluation will be conducted according to standard international guidelines using the 8th edition of the tumour/node/metastasis (TNM) classification and staging system of malignant tumours,(94, 95) with modifications.
The term Mx will be used to refer to patients with indeterminate or insufficient evidence of metastasis.

TNM Clinical Classification	
T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
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†,‡,§ and/or perforates visceral peritoneum
T4a	Tumour perforates visceral peritoneum
T4b	Tumour directly invades other organs or structures

TNM Clinical Classification	
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumour deposit(s), i.e. satellites,‖ in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue *without* regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
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 organ involvement
MX	Indeterminate or insufficient evidence of metastasis

T3 Stage	Depth of invasion beyond the muscularis propria, in mm
T3a*	< 1
T3b	1–5
T3c	6–15
T3d	> 15

*This subclassification, based on pretreatment decision MRI evaluation, is clinically valuable and can be used also in the histopathological classification, although it is not validated nor incorporated in any of the TNM versions

Appendix 2 – Common Toxicity Criteria Gradings

AEs will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

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

Appendix 3 – RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Perineal skin reactions due to radiotherapy should be graded using the modified RTOG/EORTC Late Radiation Morbidity Scoring system, available on the Radiation Therapy Oncology Group website. The following address was correct when this version of the protocol was approved: https://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx

Grade	**0**	**1**	**2**	**3**	**4**	**5**
Skin reactions	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	Death related to radiation

Appendix 4 – Surgical Morbidity Gradings

Surgical morbidity will be recorded post-operatively until 30 days after surgery and classified according to the Clavien-Dindo system.(90, 91)

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Appendix 5 – Definition of Adverse Events:

Term	Description
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Coordinating Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that at any dose: • Results in death (unrelated to original cancer) • Is life-threatening* • Requires hospitalisation** or prolongation of existing inpatients´ hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator** Comments:

	The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. **Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
Serious Adverse Reaction (SAR)	An Adverse Reaction which also meets the definition of a Serious Adverse Event.
Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SmPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

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