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), Aarhus (Denmark), Stockholm (Sweden) and Leuven (Belgium)
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 complete 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 standard surgery comparator (phase II: randomised comparison; phase III: non-randomised comparison):** • 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 24 months measured using the validated Decision regret scale questionnaire **C) Secondary endpoints 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. Randomised (phase II data) and non-randomised (phase III data) comparisons 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 (or TME at the investigator's discretion).

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.
	  ○ Poor response (see protocol) – convert to TME surgery.
	  ○ 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.
	  ○ Complete response (see protocol) – watch and wait strategy.
	  ○ Does not meet criteria for complete response – transanal local excision using TEM or equivalent surgical platform. TME will be allowed when considered in the best interest of the patient at the investigator's discretion.
	• 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. **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. Analysis of the phase II outcomes will be restricted to patients recruited during the phase II component of the trial. Analysis of the phase III outcomes will include all the relevant patients recruited during both the phase II and phase III components of the trial.
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 according to the latest protocol version. Further follow-up beyond 36 months will be according to national guidelines. For UK patients, overall survival data up to 60 months will be collected.