Scandinavian Surgical Outcomes Research Group

SAVE THE RECTUM BY WATCHFUL WAITING AFTER (CHEMO)RADIOTHERAPY OR TOTAL MESORECTAL EXCISION FOR EARLY RECTAL CANCER?

-NEXT GENERATION STAR-TREC

2025-522955-25-00

A TRIAL WITHIN THE SCANDINAVIAN SURGICAL OUTCOMES RESEARCH GROUP

Trial protocol

Trial ID:	NG-ST
EU Trial number:	2025-522955-25-00
Version number:	1.0
Date:	13-Oct-2025
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REVISION HISTORY

Protocol version	Date of issue	Summary of changes
1.1	**2025-12-10**	Addition of statistical considerations and sample size calculation

SIGNATURE PAGE

Sponsor

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this trial. I will submit the protocol and all other important trial-related information to the responsible investigator(s) so that they can conduct the trial correctly. I am aware that it is my responsibility to keep the staff members who work with this trial informed and trained.

4 Aug 2025

Eva Angenete

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the trial. By signing my name below, I agree to conduct the trial in compliance with this clinical trial protocol, the EU Regulation on clinical trials of medicinal products for human use (EU 536/2014), the Declaration of Helsinki, ICH-GCP (Good Clinical Practice) guidelines and the current national regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important trial-related information to the staff members and investigators who participate in this trial, so that they can conduct the trial correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this trial informed and trained.

I am aware that quality control of this trial will be performed in the form of monitoring and eventual audit and inspection.

4 Aug 2025

CONTACT INFORMATION

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LIST OF USED ACRONYMS AND ABBREVIATIONS

Abbreviation	Term/Explanation
ADL	Activities of Daily Living
ALT	Alanine Transaminase
AE	Adverse Event
AR	Adverse Reaction: any unfavourable and unintended reaction to an investigational medicinal product, regardless of dose
ASR	Annual Safety Report = the annual safety report for reporting to authorities. In Sweden this is the Swedish Medical Products Agency via CTIS
Bd	Bis Die (twice daily)
CBCT Voltage	Cone Beam Computed Tomography voltage. The voltage used in CBCT is usually in the range of 120-140 kV.
CRP	C-Reactive Protein
CRT	Chemoradiotherapy
cCR	clinical Complete Response
CRF	Case Report Form
CT	Computerized Tomography
CTIS	Clinical Trials Information System = Centralized EU database/portal for application and communication with authorities concerning clinical trials. In Sweden this includes the Swedish Medical Products Agency and the Swedish Ethical Review Authority.
CTR	EU Regulation 536/2014, also called CTR, Clinical Trials Regulation
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour Deoxyribonucleic Acid
DPYD	Dihydropyrimidine Dehydrogenase
DSUR	Development Safety Update Report = the standard which should be used for annual safety reporting to authorities
EMVI	Extramural Vascular Invasion
EORTC	European Organization for Research and Treatment of Cancer
FFPE	Formalin Fixed Paraffin-embedded
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
Gy	Grey, the unit of ionizing radiation dose in the International System of Units (SI), defined as the absorption of one joule of radiation
H&E	Haematoxylin and Eosin
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ITT	Intention-to-treat = including all data from all subjects who have participated in the trial
LARS	Low Anterior Resection Syndrome
Läkemedelsverket	Swedish Medical Products Agency – the national authority responsible for regulation and surveillance of the development, manufacturing and sale of medicinal products

Member State	European Union (EU) Member state where an application for authorisation of a clinical trial or of a substantial modification has been submitted.
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
OAR	Organs at Risk
PP	Per Protocol analysis = including only data from subjects who have completed the trial completely in accordance with the protocol, with no deviations from the protocol
QoL	Quality of life (here often health related quality of life, but not excluding global quality of life)
RSI	Reference safety information. A list of all known serious adverse reactions for the investigational medicinal product, including severity and frequency of the adverse reaction. The RSI is contained in the Summary of Product Characteristics or IB and is used to determine which adverse reactions should be reported as suspected unexpected serious adverse reactions (SUSARs).
SAE	Serious Adverse Event: Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death
SAR	Serious Adverse Reaction
SCRCR	Swedish ColoRectal Cancer Registry
SP or SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction: This is an event that is likely related to the investigational medicinal product but with unexpected occurrence. An adverse reaction is unexpected if its nature or seriousness is not consistent with the information on the product in the RSI.
T1	Tumour invading the submucosa
T2	Tumour invading the muscularis propria
T3	Tumour invades into subserosa or into non-peritonealised pericolic or perirectal tissues
T4	Tumour perforates visceral peritoneum (4a) and/or directly invades other organs or structures (4b)
TEM	Transanal Endoscopic Microsurgery
TME	Total Mesorectal Excision
ULN	Upper Limit of Normal

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1.0 SYNOPSIS

EU Trial number:	2025-522955-25-00
Title:	Next generation StaR-TREC -Save the rectum by watchful waiting after (chemo)Radiotherapy or Total mesorectal excision for early REctal Cancer?
Trial ID:	NG-ST
Short background/ Rationale/Aim:	In patients with a newly diagnosed early rectal cancer the primary treatment is surgery without previous neoadjuvant treatment. However, the surgical treatment is associated with complications and if surgery could be avoided maintaining curative intent it is possible that QoL could be improved. One way of achieving this goal is to treat patients with chemoradiotherapy prior to planned surgery. If the patient responds with a clinical complete response (cCR), leaving no visible tumour surgery could be avoided. This is often called organ preservation. In the international multicentre randomized study, STAR-TREC (NCT02945566**)**, patients were offered the choice of choose surgical treatment or possible organ preservation. Those who preferred organ preservation were randomised 1:1 between (i) organ preservation with mesorectal Chemoradiotherapy (CRT) versus (ii) organ preservation with mesorectal Short Course Radiotherapy (SCRT). The trial closed patient entry in end of March 2024 after having randomized the planned number of patients (in the combined phase II and III a total of 344 patients). IN the experience with the experimental treatments were that they were well tolerated by patients. Many patients were interested in the possibility to participate in the study. One year follow-up indicates that CRT renders almost 60% of patients a clinical complete response (with the addition of local excision this number was increased to 79%). In light the emerging demand from patients to offer the possibility of a non-surgical option to patients with early tumours until the results from the STAR-TREC trial are available this study has been developed. Organ preservation without detailed specification is included as a possibility in the recent guidelines for treatment of colorectal cancer in Sweden. In consensus in the oncologic and surgical community in Sweden mesorectal chemoradiotherapy has been suggested as a treatment option to standard rectal resection.
Primary objective:	Can mesorectal chemoradiotherapy achieve clinical complete response in early rectal cancer that is sustainable so that patients defer/avoid surgery?
Secondary objectives:	Oncologic: Local recurrence, mortality and overall survival Surgical: Complications and hospital stay Patient reported outcomes: Quality of life, urinary function, sexual function, bowel and stoma function

	Health economy
Primary endpoint:	Clinical complete response rate evaluated by MRI and endoscopy at one year (i.e. patients that have not undergone surgery)

Secondary endpoint:	• Oncologic:
	  ○ Clinical complete response rate without surgical intervention at three years
	  ○ Local recurrence at three years
	  ○ Mortality at three years
	  ○ Overall survival at three years
	• Surgical
	  ○ Surgical morbidity measured as Comprehensive Complications index at 90 days after surgery (if performed)
	  ○ Total length of hospital stay during the first year
	  ○ Outcome after surgery (Histopathological assessment of the resected rectal specimen to report (a) Presence of clear margins (>1mm from excision border to tumour edge), (b) TNM staging.)
	• Patient reported outcomes (all measured Baseline, post treatment, at surgery if applicable and at one, two and three years)
	  ○ Quality of life
	  ○ Urinary function
	  ○ Sexual function
	  ○ Bowel and stoma function
	Health economic analysis at three years

Trial design:	National, multi-centre, open-label, prospective trial. Patients will choose possible organ preservation or standard surgery. Those who prefer possible organ preservation will be offered treatment according to the experimental arm of the STAR TREC trial: mesorectal Chemoradiotherapy (CRT). Those who prefer standard surgery or have no preference will undergo standard Total Mesorectal Excision (TME) surgery without neoadjuvant radiotherapy treatment.
Trial population:	Subjects referred to either a colorectal surgeon or the colorectal cancer multidisciplinary team (MDT) with suspected early stage rectal cancer (T1-T3bNx/N0). Diagnosis must be confirmed with a biopsy prior to study entry.
Number of subjects:	Due to the study design the number of patients to be included has not been fixed, but it is estimated to be at least 60-80 patients during the period until STAR-TREC data will be available
Inclusion criteria:	• Biopsy proven adenocarcinoma of the rectum < 12 cm • Magnetic Resonance Imaging (MRI)-staged TT1-3b, N0, MX/M0 rectal tumour • MDT determines that the following treatment options are all

	reasonable and feasible: TME surgery or CRT • Eastern Cooperative Oncology Group (ECOG) performance status 0-1 • Willing and able to consent
Exclusion criteria:	• 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) • No residual luminal tumour following endoscopic mucosal resection or similar local excision • 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 • Medication with coumarin-derivative oral anticoagulants that cannot be stopped or substituted by low molecular weight heparin • Medication with metronidazole, phenytoin, sorivudine or its analogues, such as brivudine • Pregnancy or breast feeding • Age <18 years
Intervention:	This is a low intervention trial as the investigational medicinal product (Capecitabine) is already authorized, used according to the terms in its marketing authorization to the same diagnosis but at a different tumour stage than standard and the complementary diagnostic procedures do not contribute to the risk or burden to subject safety compared to normal clinical practice. Patients will choose organ preservation or standard surgery. Those who prefer organ preservation will be treated with **mesorectal CRT** Those who prefer standard surgery or have no preference, will undergo standard TME surgery without neoadjuvant treatment. They will be asked to participate in the QoL part of the study, while the remainder of the data will be extracted from the national quality registry, the Swedish ColoRectal Cancer Registry (SCRCR) **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.

	The **first assessment after treatment is at 6-8 weeks** (from end of chemoradiotherapy) using composite clinical, endoscopic and MRI based assessment will identify the minority of non-responders who should convert to TME surgery. **Patients demonstrating a clinical Complete Response (cCR) after chemoradiotherapy 6-8 weeks will be offered to enter the national watch and wait program and followed accordingly in the WoW study NCT03125343 (3, 6, 9, 12, 15, 18, 21 and 24 months and then every 6 months for another 3 years and then yearly for five more years).** If near complete response there will be a re-evaluation after **12 weeks** after chemoradiotherapy to determine if the criteria for clinical complete response (cCR) are met. Regardless of timepoint, patients who achieve CR may progress directly to active surveillance. Those who do not fulfil the criteria for CR will progress to TME-surgery.
Investigational medicinal product(s), dosage, administration:	Capecitabine: 825 mg/m² administered orally twice daily 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.
Ethical considerations, benefit/risk:	The treatment suggested has been evaluated at one year after finalized treatment with little known severe side effects. The benefit for the patients is that the treatment is offered as it is yet to be standardized in Sweden according to national treatment guidelines. Possible risks include increased risk for complications if surgery is deemed necessary, but according to previous publications this risk is small.
Planned duration of the trial:	About two-year inclusion, and at least three-year follow up after inclusion of the last patient.

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2.0 BACKGROUND AND RATIONALE

2.1 Rectal cancer and standard treatment

Rectal cancer is a common cancer with about 2000 new patients diagnosed yearly in Sweden. Survival and risk for local recurrence (5-9%) have improved over the last decades due to both improved surgical technique and preoperative treatment (1-7).

Standard primary radical surgery (Total Mesorectal Excision (TME)) is the evidence-based oncologically effective treatment for early-stage rectal cancer; only 2% and 12% of patients experience local or distant failure respectively (2). It entails removing the bowel including the surrounding fat and lymphatic tissue (mesorectum). However, resection of a low rectal tumour may require a permanent stoma, and many more patients will need a temporary stoma, some of which are not reversed. Complications associated with rectal cancer surgery include anastomotic leakage, which is a common complication even in non-irradiated patients, as clinical leaks amounted to 16% in the Dutch TME trial (8). Pelvic dissection may inadvertently cause autonomic nerve damage leading to urinary incontinence or retention (25%-34%) and sexual dysfunction (9-11). 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(12-14).

It is possible that radical surgery, may not be the optimal method of treatment for early tumours. Early rectal tumours can be locally excised through the anus with low morbidity and mortality using Transanal Endoscopic Microsurgery (TEM) or endoscopic submucosal dissection (ESD) (15). Morbidity and mortality after local excision are lower than after radical resection, but the long-term results have been inadequate with local recurrence rates ranging from 5% to 28% for T1 lesions, and from 11% to 45% for T2 lesions (16, 17). The problem is that these rates of recurrence are higher than would be expected with radical resection, although some registry-based data indicate that appropriate right selection of patients might improve these results(18). Omission of total mesorectal excision risks leaving behind microscopic lymph node metastases, a potential cause of local failure. It is difficult to predict the risk of lymph node involvement although there is data indicating that the risk increases with depth of wall penetration, but there can be lymph node involvement even in patients with only T1 tumours, risk factors for this includes lymphovascular invasion, tumour budding and perineural invasion. 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 (19).

2.2 Neoadjuvant (chemo)radiotherapy

Neoadjuvant (preoperative) radiotherapy has been shown to reduce local recurrence in several randomized trials (20). The two most common schedules for this treatment are preoperative chemoradiotherapy (45-50.4 Gy in combination with fluoropyrimidine based chemotherapy) and short course hypofractionated radiotherapy (25Gy in five fractions). No significant difference in local recurrence rates has been reported between the two types of schedules (21, 22). Short course radiotherapy with a delay to surgery has been studied in the Stockholm III trial which demonstrated low toxicity and a 12.5% pathological complete response (pCR) rate (23).

Although the main aim of neoadjuvant treatment firstly is to reduce the risk for local recurrence after surgery, achieving a complete removal of the tumour, a pathological

complete response (pCR) is sometimes possible. Data indicates that if a pathological complete response is achieved disease-free survival is improved compared to patients with no or little response to neoadjuvant treatment (24-26).

It has been suggested that if a clinical complete response (cCR) is achieved, surgery is not necessary, and a strategy of organ preservation could be adopted. However, the neoadjuvant must treatment eradicate all tumour tissue to achieve organ preservation. In more advanced rectal cancer this occurs after neoadjuvant treatment in about 15-20% of all tumours, thus making deferral of surgery possible. This is mainly referred to as *opportunistic* organ preservation performed in Sweden only within the framework of a study protocol (the WoW study, NCT03125343).

In Brazil this approach has been tested in selected cases since 2004 (27). It has since been reported in selected cases from all over the world collected in an international watch and wait registry, indicating that it can be possible to defer surgery if signs of cCR are seen after neoadjuvant treatment (28). In a pooled dataset including 2323 patients a correlation was found between the clinical T-stage and the pCR rate (cT1: 58%, cT2: 28%, cT3: 16% and cT4: 12%) (25). Thus, the success rate of achieving a clinical complete response after radiotherapy treatment will be highly dependent upon tumour stage. The data indicate that with appropriate selection neoadjuvant treatment may be of particular benefit to patients with early tumours.

2.3 Neoadjuvant treatment in early rectal cancer with the aim to avoid surgery

There have been some studies, mainly prospective, non-randomised phase II studies that have evaluated use of (chemo)radiotherapy in the context of early-stage rectal cancer for the purpose of achieving a clinical complete response and organ preservation. These studies generally supplemented the neoadjuvant treatment with local transanal excision and or radiotherapy boosts of the area of the bowel wall originally occupied by tumour. The studies demonstrated high rates of organ preservation and infrequent pelvic cancer recurrence; but often at the cost of treatment related toxicity (29-34). It has been suggested that modifying the approach to local excision could improve results, either only performing local excision if residual tumour is present as carried out in the recent STAR-TREC trial (35) or in all patients (sometimes only removing a scar) as in the recently published TAUTEM (Chemoradiotherapy and Local Excision vs Total Mesorectal Excision in T2-T3ab, N0, M0 Rectal Cancer). In the TAUTEM study 17 hospitals in Spain participated and all but one patient in the chemoradiotherapy arm underwent TEM(36). In the STAR-TREC trial both chemoradiotherapy and short course radiotherapy with a delay to surgery was used(35) and patients with incomplete response were treated with TEM if there were signs of a more advanced tumour, these patients were referred to radical surgery. Three centres in Sweden participated in the study and results presented at the ESTRO congress in Vienna report cCR after 5x5 Gy of 27% compared to 57% after CRT. Addition of local excision after near complete response resulted in a watch and wait strategy at one year of 61.5% after 56x5Gy compared to 79.8% for patients treated with CRT.

Another option that has been suggested consists of an endoluminal brachytherapy approach which might achieve better tumour response with lesser toxicity (37). The OPERA included patients with T2-T3b tumours with minor lymph node involvement (N1<8 mm) and all patients received chemoradiotherapy. They were then randomized to either a boost of external

beam radiotherapy (9 Gyx5) or brachy radiotherapy (90Gy/3 fractions). They found that 64% of patients with external beam radiotherapy achieved a clinical complete response, compared to 92% after brachy radiotherapy. The 5-year local regrowth was 39% vs 17%, and some patients had their local regrowth after 3 years, indicating that long-term follow-up may be necessary. There are indications that patients that undergo brachy radiotherapy and then have incomplete response have very poor bowel function suggesting that studies are required to ascertain that patients receive correct information for shared decision making (38).

In summary there seems to be sufficient evidence that some patients will achieve clinical complete response after chemoradiotherapy with a long-term positive oncologic outcome (25), but long-term morbidity is not sufficiently described to date. This treatment will increase the risk for postoperative complications and increased risk for affected bowel function after both local excision and TME-surgery. Local excision may not always be adequate to treat insufficient response to chemoradiotherapy. Presently in Sweden there are no available treatment options apart from radical surgery (as recommended in the Swedish National Treatment Guidelines for Colorectal cancer) for patients with early rectal cancer while waiting for the long-term results from the STAR-TREC trial. The CORRECT trial has commenced in Stockholm and Uppsala in 2025 offering treatment options with contact therapy (brachy radiotherapy).

2.4 Rationale and design of the Next generation study awaiting the results from the STAR-TREC study

In light of the promising results from smaller studies, and the positive experience from treatments centres within the STAR-TREC trial this study aims to offer at treatment option to patients with early rectal cancer in a prospective phase II study to enable evaluation of results, and to enable comparisons with results from present and future studies until results from the STAR-TREC trial are published. The first results presented at ESTRO 2025 indicate that 57% of patients that received CRT maintained a clinical complete response one year after treatment compared to 27.3% in the arm with 5x5 Gy (https://user-swndwmf.cld.bz/ESTRO-2025-Abstract-Book). The dosage of Capecitabine at 825mg/m^2 for five days per week has been chosen to mimic the STAR-TREC study.

The STAR-TREC trial included patients with a radiological staging Magnetic Resonance Imaging (MRI)-stageTX/T1-3b, NX/N0, MX/M0 rectal tumour. Exclusion criteria were designed to avoid including patients with known risk factors for locoregional relapse following rectal cancer treatment. This study will use the same inclusion criteria, and similar follow-up routine. Patients who choose standard treatment i.e. radical surgery (TME-surgery) will be the control arm.

The choice to refrain from local surgical resection of a possible small regrowth or insufficient response lies in a combination of clinical observations of morbidity and insufficient clinical experience at the study sites. It may be reconsidered when the long-term results from the STAR-TREC study are available, and the use of local excision is supported by the recent data from the TAUTEM trial where mesorectal CRT and TEM were found non-inferior to standard TME resection (36).

2.1.5 Patient involvement

The study has been discussed and modified in collaboration with patient representatives from the Swedish stoma association ILCO.

3.0 BENEFIT-RISK EVALUATION

3.1 Benefits

The possible benefits for patients entering this study include

- avoiding surgery and surgery related complications including surgical infections, small bowel obstruction, cardiopulmonary complications and others
- possibly improved bowel function due to deferring surgery
- possibility to avoid a stoma that may improve quality of life.

3.2Risks

Possible risks are:

- Patients enter the study hoping to avoid surgery, but many will still require surgery to achieve cure. This could be difficult to accept and may lead to disappointment. The best way to mitigate this is probably by informed consent and providing support.
- As some patients will require surgery it could be considered that they are over-treated with chemotherapy and radiotherapy before surgery. This may increase the risk for complications postoperatively.
- The rigid follow-up if surgery is avoided in a watch and wait setting might increase the risk of fear of recurrence or anxiety, although data are scarce (39, 40). This is mitigated by support and information.
- Chemotherapy may induce side-effects: hand-foot syndrome, diarrhoea, vomiting, nausea, stomatitis, abdominal pain, anorexia, fatigue, and asthenia. Less common side effects include cardiotoxicities, cytopenia, infections, thrombophlebitis, deep vein thrombosis, pulmonary embolism, kidney failure, liver toxicity, skin reactions, hypersensitivity reactions and toxic leukoencephalopathy.
- Radiotherapy of rectal cancer, 50 Gy/25 Gy, can cause acute and late side-effects such as increased urinary and bowel frequency, pain in the lower abdomen and anus, anal discharge, sexual dysfunction, infertility, colitis, pelvic stiffness/pain, secondary malignancies. In this study, the treatment volume is significantly smaller compared with radiotherapy given in advanced rectal cancer. The concept of reduced treatment volume is new and previously tested only in the STAR-TREC trial, preceding this study. Interim data from the STAR-TREC trial show minimal short-term treatment-related toxicity. In patients that have a complete tumour response with radiotherapy alone, the overall risk of late morbidity is assessed to be lower compared with the patients undergoing up-front TME-surgery according to clinical routine. In patients that will need TME surgery after radiotherapy the radiotherapy will add up to the acute and late morbidity. Given the reduced treatment volumes and moderate radiotherapy doses, the acute and late toxicity is assessed to be manageable.

4.0 TRIAL OBJECTIVES

Investigate if using chemoradiotherapy 2 Gy x 25 with Capecitabine 825 mg/m^2 and a limited clinical target volume (CTV) will obtain a clinical complete response rate of 50% or more in patients with TX/T1-3b, NX/N0, MX/M0 rectal tumours.

The aim is to provide a treatment option to surgery to patients with early rectal cancer that fulfil the inclusion criteria for the now closed STAR-TREC study. This will enable a safe implementation with a control of outcomes and treatment regimens.

4.1 Primary objective

The primary objective of this trial is to achieve a sustained clinical complete response rate in patients 1 year after treatment.

4.2 Secondary objectives

The secondary objectives of this study include oncologic safety, treatment related safety and functional outcome including quality of life (QoL).

4.3 Primary endpoint

Primary variable: clinical complete response rate. Measured as the ratio of patients with a non-operative approach at onset that after evaluation by a combination of MRI, clinical and endoscopic examination have a clinical complete response at 1 year.

4.3. Secondary endpoint

The secondary endpoints for the study are:

- Oncological:
  - local recurrence
  - local regrowth
  - Survival (overall)
  - Metastases
  - Organ preservation rate
  - clinical complete response rate
- Surgical
  - morbidity measured with Comprehensive Complications Classification Index (41)
  - total length of hospital stay,
  - radical resection (R0) after surgery
- Quality of life
  - Urinary function
  - Sexual function
  - Bowel function
  - presence of a stoma
- Health economic evaluation.

5 TRIAL DESIGN AND PROCEDURES

5.1 Overall trial design

The study design is a national multi-centre prospective non-randomized phase IV cohort study. Planned centres are Sahlgrenska University Hospital, Skåne University Hostpital, Stockholm South General Hospital. It is an initiative from the surgical and oncological community in Sweden to offer patients a choice of treatment before solid scientific evidence is present to support either treatment option. It is a low-intervention clinical trial as the investigational medicinal product Capecitabine is authorized and used according to the terms in its marketing authorization to the same diagnosis but at a different tumour stage than standard. The complementary diagnostic procedures are not considered to contribute to the risk or burden to subject safety compared to normal clinical practice.

Patients who meet inclusion criteria will be offered neoadjuvant treatment to defer/avoid surgery or TME surgery upfront.

Those who prefer organ preservation will be treated with **mesorectal chemoradiotherapy.**

Those who prefer standard surgery or have no preference, will undergo standard TME surgery without neoadjuvant treatment. They will be asked to participate in the QoL part of the study, while the remainder of the data will be extracted from the national quality registry, the Swedish ColoRectal Cancer Registry (SCRCR)

For possible organ preservation long course concurrent chemoradiation will be performed (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.

The **first assessment after treatment is at 6-8 weeks** (from end of chemoradiotherapy) using composite clinical, endoscopic and MRI based assessment will identify the minority of non-responders who should convert to TME surgery. Patients demonstrating a clinical complete response (cCR) after chemoradiotherapy 6-8 weeks will be offered to enter the national watch and wait program and followed accordingly in the WoW study NCT03125343 with endoscopy and MRI and clinical follow-up accordingly (at present 3, 6, 9, 12, 15, 18, 21 and 24 months and then every 6 months for another 3 years and then yearly for five more years).

If **near complete response** there will be a re-evaluation after **12 weeks** after chemoradiotherapy to determine if the criteria for clinical complete response (cCR) are met.

Patients who achieve cCR may progress directly to active surveillance and included in the Swedish Watch and Wait study (WoW, NCT03125343). Clinical and radiological follow-up at 3, 6, 9, 12, 15, 18, 21 and 24 months. First year registered in CRF in this study too, after that follow-up at 1, 2 and 3 years.

Those who do not fulfil the criteria for cCR will progress to TME-surgery. Follow-up at 1, 2 and 3 years.

Time points for follow up and collection of data into CRF

1. Inclusion
2. Start of neoadjuvant treatment
3. Evaluation after neoadjuvant treatment
4. Second follow-up after neoadjuvant treatment if applicable
5. Third follow-up after neoadjuvant treatment if applicable
6. Surgery if applicable
7. Postoperative hospitalization if applicable
8. 1 month follow-up after surgery
9. 1 year after diagnosis
10. 2 years after diagnosis
11. 3 years after diagnosis
12. 5 years only through SCRCR and Swedish Cause of Death Registry

5.2 Procedures and flow-chart

See table 1 for details on each visit.

Each follow-up visit may vary 2-3 weeks depending on availability to radiology, endoscopy and clinical visit.

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	Screening	**Neoadjuvant treatment**				**Surgery** if applicable[4]	Follow-up				
	At/before first visit in surgical clinic	First visit in oncology clinic	End of CRT treatment	6-8 weeks after end of neoadjuvant treatment if not cCR	10-12 weeks after end of neoadjuvant treatment if not cCR	Surgery	Hospital stay after surgery, follow-up 1 month after discharge	3 months after cCR	6 months after cCR	9 months after cCR	12 months after cCR or surgery	**Every 3 months 12-24 monts after cCR**
Written informed consent	X											
Medical history[1]	X											
ECOG performance status	X		X									
Digital rectal examination	X			X	X			X	X	X	X	**X**
Physical examination	X											
Colonoscopy[2]	X											
Confirmed diagnosis of adenocarcinoma[3]	X	X										
Computerized Tomography (CT) scan thorax, and CT or MRI abdomen	X										X	
High resolution MRI pelvis	X			X	X			X	X	X	X	
MDT review	X											
Blood sample	X					X						
Preparation of FFPE tissue blocks and biopsies [3]	X					X						
QoL questionnaire	X			X							X	
Toxicity related to (chemo)radiotherapy registered in CRF			X					X				
Complications related to surgical procedure according to Clavien-Dindo												
Sigmoidoscopy								X	X	X	X	**X**
Survival status		X	X				X	X				

[1]Medical history includes details of current colorectal cancer, previous and current medical conditions and previous treatments received. [2] Colonoscopy should be performed either prior surgery or within three months after surgery. At least one colonoscopy to be performed within the first 3 years of follow-up and according to national guidelines. [3] Biopsies taken and sent to routine pathology department (note name of pathology department in CRF). [4]Surgery can be performed either immediately or when a cCR cannot be achieved or if there is suspicion of regrowth.

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	Follow-up					Not registered in eCRF but according to clinical routine	Not registered in eCRF but according to clinical routine	Not registered in eCRF but according to clinical routine	Not registered in eCRF but according to clinical routine
	15 months after cCR	18 months after cCR	24 months after cCR or surgery	30 months after cCR	36 months after cCR or surgery	42 months after cCR	48 months after cCR	54 months after cCR	60 months after cCR
Written informed consent									
Medical history[1]									
ECOG performance status									
Digital rectal examination	X	X	X	X	X	X	X	X	X
Physical examination									
Colonoscopy[2]									
Confirmed diagnosis of adenocarcinoma[3]									
Computerized Tomography (CT) scan thorax, and CT or MRI abdomen			X		X		X		X
High resolution MRI pelvis	X	X	X	X	X	X	X	X	X
MDT review									
Blood samples			X		X				
Preparation of FFPE tissue blocks and biopsies [3]									
QoL questionnaire			X	X	X				
Toxicity related to (chemo)radiotherapy registered in CRF			X		X				
Complications related to surgical procedure according to Clavien-Dindo									
Sigmoidoscopy	X	X	X	X	X	X	X	X	X
Survival status	X	X	X	X	X	X	X	X	X

5.3 Biological sampling procedures

Pre-therapeutic biopsies will be taken during endoscopy/rectoscopy during examination of the tumour in the outpatient clinic. Biopsies will be sent according to local routines to the pathology department. The name of the pathology department will be registered in the CRF. At end of inclusion in the trial blocks will be collected from the different pathology departments for analysis at Sahlgrenska University Hospital.

Biopsies will be taken from the resected specimen at surgery and sent to the pathology department. Blocks will be collected at the end of the study and sent in batches to the study centre at Sahlgrenska University Hospital and University of Gothenburg. Patients that are considered complete responders after treatment will not be subject to further biopsies.

Blood samples will be collected at baseline, surgery and at each follow-up and stored according to a separate standard operating procedure. They will be sent for analysis to the study centre at Sahlgrenska University Hospital and University of Gothenburg.

5.3.1 Handling, storage and destruction of biological samples

All biopsies are sent to the routine pathology department. Blocks will be collected from the diagnostic procedure as well as when applicable from the surgical specimen.

Formalin fixed paraffin embedded biopsies will be stained according to our previously published multicolour panel (42). They may also be subject to assembly of tissue micro array prior to staining.

5.3.2. Total volume of blood per subject

The total volume of blood taken from each subject during the trial is a maximum of 50 ml per sampling and a total 200-250 ml/patient during the study.

5.3.3 Biobank

All samples taken in this trial, covered by the Biobank Act are registered in a biobank and handled according to the current national laws and regulations. The samples are coded to protect the subject’s identity. All samples and the identification/code lists are stored securely and separately to prevent access by unauthorized persons.

5.4.1 Start of the clinical trial

The start of the clinical study is defined as the first visit of the first subject at the surgical department at any of the recruiting sites.

5.4.2 Temporary halt or early termination

The start of the study is defined as the first visit of the first subject at the surgical department at any of the recruiting sites. Sponsor will report the start of the trial through notification in the Clinical Trial Information System (CTIS) within 15 days.

The study may be prematurely terminated for safety reasons affecting the risk-benefit balance or if the recruitment of subjects cannot be completed within reasonable time. Decisions on premature termination are taken by the sponsor. The Competent Authorities should be informed as soon as possible via CTIS, but no later than 15 days after trial suspension.

If the study is prematurely terminated or suspended, the investigator should immediately inform the subjects and ensure appropriate treatment and follow-up.

5.4.3 End of clinical trial

The trial ends when the last subject has completed the last follow-up of three years.

6.0 SUBJECT SELECTION

6.1 Inclusion criteria

To be included in the trial, subjects must meet all of the following criteria:

- The subject has given their written consent to participate in the trial
- Be 18 years or older
- Have an adenocarcinoma verified tumour within the rectum below 12 cm from anal verge
- Have a tumour stage of TX/T1-3b (regardless of tumour size)
- Have no nodal metastases (NX/N0)
- Have no distant metastases (MX/M0)
- Have an Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- For female subjects of childbearing potential:
    - 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 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

6.2 Exclusion criteria

Subjects must not be included in this trial if any of the following criteria are met:

- Give no informed consent
- No biopsy confirmed rectal cancer (adenocarcinoma)
- Have a recurrent rectal cancer
- An age below 18
- Have 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
- Have unequivocal evidence of metastatic disease (includes respectable metastases) (Patients with equivocal radiological lesions (e.g. retroperitoneal, liver, lung) that are not classified as M1 are eligible if agreed by MDT)
- Have an MRI node positive tumour (≥N1, defined by protocol guidelines) (Patients with equivocal radiological findings that are either classified as NX or N0 are eligible)
- Have MRI extramural vascular invasion (mriEMVI) positive (defined by protocol guidelines)
- Have a threatened mesorectal fascia (≤1 mm on MRI or ERUS)
- Have no residual luminal tumour following endoscopic resection prior to first visit at surgical department

- Have contraindications to radiotherapy including previous pelvic radiotherapy
- Have uncontrolled cardiorespiratory comorbidity (includes patients with inadequately controlled angina or myocardial infarction or arrhythmia within 6 months prior to trial entry)
- Have known complete dihydropyrimidine dehydrogenase (DPYD) deficiency
- Have known Gilbert's disease (hyperbilirubinemia)
- Have been 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
- Are taking metronidazole, phenytoin or sorivudine or its chemically related analogues, such as brivudine, within 4 weeks of trial entry (see Section 8.3.5 for further details)
- Are Pregnant or lactating woman
- Have history of severe and unexpected reactions to fluoropyrimidine therapy

6.3 Screening and inclusion

Subject eligibility is established at the multidisciplinary meeting that often precedes the first outpatient meeting after a diagnosis has been established. If the subject comes to the outpatient clinic prior the multidisciplinary meeting, there is a possibility to screen for inclusion and give oral and written information. This procedure is decentralized and can be performed at any hospital that refers patient to any of the hospitals including in the clinical trial. A member of the direct clinical care team will always make the first approach to the patient.

The subject will then be given adequate time to consider the study and agree to participate before being referred to the hospital including in the clinical trial. A treatment plan will be set, and the patient will sign informed consent and can then either receive the treatment according to the study protocol at the hospital participating in the clinical trial or in a decentralized manner.

All clinical information entered into CRFs will be entered by the hospitals participating in the clinical trial regardless of decentralized process or not.

Individuals who do not wish to enter the study will be offered standard treatment according to the Swedish National Treatment Guidelines for Colorectal Cancer, i.e. TME surgery. The experimental organ saving treatment is not offered outside a study setting unless unfit for primary TME surgery.

Details of all participants approached about the trial will be recorded on the Participant Screening Log. The following data will be recorded:

1. Sex
2. Age
3. Clinical TNM according to TNM v8
4. Planned oncologic and surgical treatment

In addition – all patients treated at the participating hospitals are registered in the Swedish ColoRectal Cancer Registry (SCRCR). If necessary, missing information will be retrieved (sex, age and clinical TNM stage, type of surgery performed and recurrence data) on non-included patients using the SCRCR

6.4 Withdrawal criteria

Subjects can discontinue their participation in the study at any time without any consequence to his/her continued treatment. The investigator/sponsor can at any time terminate the study for a subject due to, e.g., unacceptable adverse events/adverse reactions or because the subject does not follow procedures in the clinical trial protocol. If the subject discontinues the trial, follow-up of this subject will be performed according to the clinic's routine.

7.0 TRIAL TREATMENTS

7.1 Description of investigational medicinal product(s)

The only Investigational Medicinal Product (IMP) used in the Next Generation ST study is capecitabine. This is a low intervention clinical study and the IMP used is standard for patients with rectal cancer.

7.1.1. Dose and administration

There is no international standard dosing for the combination of capecitabine with long course radiotherapy. The dose chosen in Next Generation ST is based on the STAR TREC study where patients received 825mg/m^2 bd five days per week.

A phenotypic or genotypic DPYD deficiency test is recommended prior to starting treatment to identify patients likely to develop severe capecitabine-related toxicities due to reduced catabolism/increased exposure. The reported DPYD result should be recorded in the CRF and will define subsequent patient management:

- Complete DPYD deficiency: Patient cannot be included in the study.
- Partial DPYD deficiency: Capecitabine starting dose to be reduced as per local guidelines

The following criteria must be met prior commencing treatment with capecitabine:

- 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 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. 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 daily within 30 minutes after the ingestion of food, 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.

7.1.2 Packaging, labelling, and handling of investigational medicinal products

Trial supplies of capecitabine for the entire treatment period will be prescribed and collected at the pharmacy during the study period. The costs for the drugs will be covered through the national drug insurance, and no drug costs will be reimbursed.

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 amended dose details in the dispensing label.

Capecitabine will be in commercial stock in standard packaging.

7.1.3 Drug accountability and treatment compliance

As this is a low- intervention clinical study we will not perform an extensive traceability rather, the responsible physician and nurse that have prescribed the chemotherapy will keep track of compliance and document if patients miss/skip a dose.

7.2 Auxiliary medicinal products

No auxiliary medicinal products are planned within the study.

7.3 Concomitant treatment of radiotherapy

7.3.1 Purpose and scope of radiotherapy guideline

This document is based on the previous radiotherapy guidelines from the STAR-TREC trial (EudraCT no 2016-000862-49)(35). The STAR-TREC study introduced the concept of mesorectal treatment planning in early rectal cancer with reduced target volumes compared to previous standard in rectal cancer irradiation. The aim of this document is to ensure uniform delivery of radiotherapy and the collection of high-quality data for study analysis.

7.3.2 Radiotherapy treatment planning

The use of Computed Tomography (CT) scan for treatment planning is considered standard practice and is a mandatory requirement. The scan limits are the superior aspect of L5 to 4 cm below the anal verge. The recommended slice thickness is 2-3 mm, but a slice thickness of up to 5 mm is accepted. The use of intravenous contrast is optional and should align with local centre policy. Magnetic Resonance Imaging (MRI) is strongly recommended for guidance in target definition.

7.3.3 Patient position and immobilisation

Patient set-up follows local routines. The supine position is recommended. If the prone position is used; belly board may be used but is not mandatory. This manual comprises no bladder or bowel protocol. Local routines should be followed, but a general recommendation is that the bladder should be comfortably filled and the rectum as empty as possible.

7.3.4 Definition of treatment volumes

All treatment volumes should be named according to current guidelines from the Radiation Safety Authority(43).

7.3.5 Gross tumour volume (GTV)

Gross tumour volume (GTV) is named GTVT_50. All macroscopic tumour is delineated on each slice. Only involved areas of the rectal wall are included. Rectal faecal contents are not to be include in the GTV.

7.3.6 Clinical target volume (CTV)

Clinical target volume (CTV) is named CTVT_50.

7.3.6.1 Superior limit

Is defined as the S2/S3 interspace. A minimum of 2 cm is required from the superior limit of the GTV to the CTV. If the tumour is localized in the upper rectum, CTV may be extended above S2/S3 interspace to achieve the 2 cm margin.

7.3.6.2 Inferior limit

Is defined as 2 cm inferior of the GTV. An exception is if the tumour is localized in the lower rectum and the CTV margin extends into the anal canal. A maximum of 1 cm of the anal canal should be included in CTV.

7.3.6.3 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 the defined by the contour used for the last carinal slice with visible rectum.

7.3.6.4 Posterior limit

Is defined as the anterior margin of the sacrum or coccyx, or the inner border of the puborectalis muscle in caudal slices.

7.3.6.5 Lateral limits

The mesorectal fascia is contoured. In the most cranial (high pelvis) and caudal slices (low pelvis) mesorectal fascia is not present. In high pelvis, the lateral border comprises the inner border of the piriformis muscle. In low pelvis, the lateral border comprises the inner border of

7.3.7 Planning target volume (PTV)

Planning target volume (PTV) is named PTVT_50. PTV margins will depend on local technique, image guidance schedule, and treatment setup procedure and uncertainties. If Cone Beam Computed Tomography (CBCT) is used for on-line imaging, the PTV margins may be reduced to 6-8 mm. If 2D kV (two-dimensional kilo voltage) imaging is used an anisotropic PTV margin is recommended: 10 mm margin in all directions except anteriorly where a 15 mm margin is recommended.

7.3.8 Organs at risk (OAR)

The following organs at risk (OAR) must always be delineated:

- Urinary bladder (Bladder)outer contour of the bladder as it appears on planning CT. The structure should be named Bladder according to established nomenclature.
- Bowel bag (BowelBag): The bowel bag is contoured superiorly from 1.5 cm above the most superior part of the PTV. Anteriorly to the inside of the abdominal wall.

Laterally, it is delineated from bowel edge to bowel edge. The posterior limit is the most posterior bowel edge. The most inferior limit includes the most inferior bowel that is not rectum or rectosigmoid junction.

- Bowel (Bowel): Individual bowel loops, excluding the rectum, is delineated within the bowel bag as defined above.
- Left and right femoral heads (FemoralHead_L; FemoralHead_R): Contoured to the most inferior extent including the lesser trochanter.

7.3.9 Dose and volume guidelines

Radiation therapy should be delivered with photon energies ≥6 MV using a linear accelerator. Volumetric modulated arc therapy (VMAT) is strongly. All fields must be treated during each treatment sessions.

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 is combined with Capecitabine 825 mg/m2 twice daily on radiotherapy treatment days.

7.3.10 Dose-volume objectives and constraints

The isocentric treatment plan is usually specified to receive 100% with the 95% isodose line encompassing the PTV and no more than +5 % and -5% inhomogeneity within the target volume. If OAR doses can be limited even further for the individual patient, without compromising target coverage, this should be attempted.

Priority	Structure	Dose-volume objectives
1	GTVT_50	D99%≥99%
1	CTVT_50	D99% ≥ 98 % Dmean ≥100 %
1	PTVT_50	D2% ≤ 105 % D98% ≥ 95 %
2	Body	D2% ≤ 105 %
3	BowelBag	V20Gy < 180 cm3 V30Gy < 130 cm3 V45Gy < 90 cm3
3	Bowel	V20Gy < 120 cm3 V30Gy < 90 cm3 V45Gy < 60 cm3
3	Bladder	V35Gy < 22% V50Gy < 7%
R*	FemoralHead_L FemoralHead_R	V25Gy <15%

*Report value

7.3.11 Treatment verification

Generally, on-treatment imaging frequency should align with local policy. However, daily on-line imaging is highly recommended since reduced margins are used in mesorectal irradiation. If daily on-line imaging with CBCT is used, smaller PTV (6-8 mm) margins may be used.

7.3.12 Radiotherapy Quality Assurance (RTQA)

7.3.12.1 Pre-trial QA

Facility Questionnaire (FQ): general and trial specific questions on equipment, software and techniques to be used for the trial.

Benchmark Outlining and Planning Cases: Each study centre will need to submit a benchmark delineation case outlined by clinical oncologist involved in the study. Additionally, a benchmark planning case will need to be planned and submitted with a plan assessment form (PAF).

7.3.12.2 On-trial QA

Radiotherapy related data should be collected and reported by each centre for every patient and transferred to the QA centre at Sahlgrenska University Hospital within 2 months after finalizing radiotherapy. The data transfer is handled through the Skandionkliniken Sharefile service (https://skandionibasa.sharefile.eu/home/shared)

A folder named NGST_XX_YYYY, where XX is the number of the study site and YYY is the patient study number, should be created and include anonymized DICOM files for planning CT images, structure set (RS), registered images, treatment plan (RP) and dose (RD). Notify the RT-QA office that patient data has been uploaded by sending an e-mail to the study specific e-mail address: **su.onk.next-generation@vgregion.se**

A safety assessment will be performed after the first 10 RT plans to confirm adherence to the protocol regarding target delineation and dose planning.

7.4 Surgery

If the patient does not achieve complete response after the second evaluation after neoadjuvant treatment surgery will be recommended. Any deviation from this will be considered a protocol violation and must be registered. It is important that the patient understand that there is an increased risk of tumour progression if surgery is not performed at this stage.

The preoperative and perioperative treatment regarding anaesthesia and antibiotics and all other details must follow local guidelines.

All patients should be given pre-operative prophylactic antibiotics and antithrombotic medication such as low molecular heparin before the start of the operation. The type of antithrombotic medication should be registered in the eCRF. Any bowel preparation performed is according to local/regional/national routine.
For the purpose of this study TME surgery is defined as previously published (44). No distinction is made between different surgical approaches. Laparoscopic, robot assisted laparoscopy, or open surgery can all be used and the choice is at the discretion of the surgeon.

7.5 Treatment after trial end

No specific treatment will be administered after the study.

8 METHODS FOR MEASUREMENT OF ENDPOINTS FOR CLINICAL EFFICACY AND SAFETY

8.1 Methods for measurement of endpoints for clinical efficiency

8.1.1 Primary endpoint

Primary variable: clinical complete response rate. Measured as the ratio of patients with a non-operative approach at onset that after evaluation by a combination of MRI, clinical and endoscopic examination have a clinical complete response at 1 year.

Definition of clinical complete response (cCR)

1. No suspicious metastatic lymph nodes or evidence of remaining tumour on MRI. In a majority a complete response on MRI will be seen as areas of homogeneous fibrosis. Absence of any remaining pathological tissue is seen in a minority of cases.
2. Endoscopic examination with white light. Presence of light/white mucosa or scar, telangiectasia. Presence of fibrosis and oedema.
3. No palpable tumour on clinical examination if the tumour was palpable initially.

Definition of near clinical complete response – possible to re-examine again after four weeks

1. The majority of the tumour is converted to fibrosis with homogeneous low signal intensity on T2-weighted images with minor areas of impeded diffusion on high b-value DWI.

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

8.1.2 Secondary endpoints

Secondary outcome	*Variable*	*Summary measure*	*Time point°*
Local recurrence	Registration in CRF	Proportion	3 years
Local regrowth	Registration in CRF	Proportion of patients that have achieved clinical complete response	1, 2 and 3 years
Surgical morbidity measured as Comprehensive Complications index°	All complications registered according to Clavien-Dindo	Median value	90 days postoperatively in cases where surgery is necessary
Organ preservation rate at 3 years	Registration in CRF	Proportion	Patients with remaining rectum without deviating stoma at three years. Regardless of function.

Clinical complete response rate	Registration in CRF	Proportion	1 and 2- and 3-years follow-up after inclusion
R0 rate among operated patients	Registration in CRF	Proportion among operated patients	1 and 3 years after inclusion, both patients with initial organ preservation and TME resection surgery
Metastases	Registration in CRF	Proportion as well as subgroup specification of location	1 and 3 years after inclusion
Total length of hospital stay	Total number of days including readmissions	Median and range	Within 365 days after diagnosis
Quality of life	Measured in QoL questionnaire	Value baseline vs follow-up. Likert scale with dichotomization	Baseline, post treatment, at surgery if applicable and at one, two and three years
Urinary function	Measured in QoL questionnaire focus on incontinence, emptying difficulties and urgency	Value baseline vs follow-up and comparing groups	Baseline, post treatment, at surgery if applicable and at one, two and three years
Sexual function	Measured in QoL questionnaire, focus on both function and quality	Value baseline vs follow-up and comparing groups	Baseline, post treatment, at surgery if applicable and at one, two and three years
Bowel and stoma function	Measured in QoL questionnaire, major LARS	Value follow-up comparing groups	Baseline, post treatment, at surgery if applicable and at one, two and three years
Patients with a stoma	Measured as number of patients with a stoma/total number of patients	Proportion	One, two, three years
Health economic analysis	EQ5D as well as cost evaluation from both societal and health care sector perspective. Will include number of days on sick leave.		3 years after diagnosis
Mortality	Registration in CRF	Proportion	3 and 5 years after diagnosis
Patient satisfaction	Decision regret form		3 years after inclusion
5- year overall survival	Registration in CRF	Proportion	5 years after inclusion

° *Comprehensive Complications* index (45)

8.1.3 Quality of life assessment

All patients will be asked to fill in a questionnaire with QoL questions including the LARS-score, Decision Regret form, EORTC QLQ C30 and CR29 as well as additional questions derived from previous studies within rectal cancer (46). The time points for QoL questionnaire collection are the same as for the radiological follow-up:

1. Baseline
2. End of CRT treatment (at 2-3 months)
3. 1 year
4. 2 years
5. 3 years

8.2 Methods for measurement of endpoints for clinical safety

See point 8.1. If there is any ambiguity in the evaluation the patient will be recommended to go to surgery to reduce the risk for insufficiently treated cancer.

9.0 HANDLING OF ADVERSE EVENTS

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

- Planned surgery (e.g. TME surgery or stoma reversal)
- Planned hospitalization
- Recurrence
- Death due to progression of the disease

Any adverse events (AE) and serious adverse events (SAE) will be reported during the trial during the first year.

9.1 Definitions

9.1.1 Adverse Event (AE)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product/the experimental treatment. Only adverse events reported spontaneously by the subject or observed by the investigator or his staff of grade 3 or 4 will be recorded.

9.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life-threatening disease, major safety finding from a newly completed animal study, etc.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

All SAEs, irrespective of relationship to the study treatment must be reported to the Datacentre.
The SAE report should include the investigator's assessment of causality. If follow-up information changes the investigator's assessment of causality, this should be noted on the SAEs occurring within 30 days after discontinuation of the study treatment should be reported.

9.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product

related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal

9.2 Assessment of Adverse Events (AE)

9.2.1 Assessment of causal relationship

The investigator is responsible for determining whether there is a causal relationship between the AE/SAE and use of the investigational medicinal product.

Consideration should be given to whether there is a reasonable possibility of establishing a causal relationship between the adverse event and the investigational medicinal product based on the analysis of the available evidence.

All AE can be categorized as either likely related, possibly related, unlikely related or not related, in accordance with the definitions below:

Likely related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational medicinal product. It is unlikely that the event can be attributed to underlying disease or other medications but is most likely caused by the investigational medicinal product and its emergence is reasonable in relationship with use of the investigational medicinal product.

Possibly related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational medicinal product. The event could be explained by the investigational medicinal product, and its emergence is reasonable in relationship with use of the investigational medicinal product, but there is insufficient information to determine the relationship. The event could be explained by an underlying disease or other medications.

Unlikely related: Clinical event, including abnormal responses from laboratory tests, unlikely to be related to the intervention/investigational medicinal product and can be reasonably explained by other medication or underlying disease.

Not related: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational medicinal product.

Those AEs which are suspected of having a causal relationship to the investigational medicinal product will be followed up until the subject has recovered or is well taken care of and on the way to good recovery (see also section **Error! Reference source not found.**, **Error! Reference source not found.**).

If the reporting investigator does not provide any information on causality, the sponsor should consult with the reporting investigator and encourage the expression of a position on this issue. The sponsor must take into account the assessment of causality provided by the investigator. If the sponsor disagrees with the investigator's assessment of causality, both the investigator's and the sponsor's views should be included in the report.

9.2.2 Assessment of intensity

Patients should be reviewed at least weekly during CRT to perform an assessment of acute toxicity. Remote toxicity assessments (e.g. over the telephone) are allowed as per local practice 4. The local team should have a structure in place that ensures that patients experiencing side effects can be seen and undergo review.

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**.

Dose modification and toxicity should be managed according to local routines. Details on toxicity is registered in CRF.

9.3 Reporting and registration of Adverse Events

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

- Planned surgery (e.g. TME surgery or stoma reversal)
- Planned hospitalization
- Recurrence
- Death due to progression of the disease

At each trial visit, adverse events (AE) are registered, starting after study start, up to and including one year after the subject has entered the study. All AE that occurs during the trial and which are observed by the investigator/trial nurse or reported by the subject will be registered in the CRF regardless of whether they are assessed as related to the investigational medicinal product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE will be made by the investigator directly in the CRF. At minimum for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE, measures and outcome.

9.3.1 Reporting of Adverse Events (AE)

All AE shall be registered in the CRF within 72 hours.

9.3.2. Reporting of Serious Adverse evets (SAE)

Serious Adverse Events (SAE) are reported to the sponsor on a special SAE form within 24 hours of the investigator being informed of the SAE.

Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available. The original SAE form should be kept in the Investigator Site File.

9.3.2. Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

Those SAE which are assessed by sponsor to be SUSAR are to be reported to the EudraVigilance database. The completed CIOMS form will be the basis for the reporting, by Swedish Medical Products Agency in the EudraVigilance database according to the specified time frames.

SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the SAE has become known to the sponsor. Relevant follow-up information is sent thereafter within an additional 8 days. Other SUSAR are reported as soon as possible and no later than 15 days after they have come to the sponsor’s knowledge.

Information about SUSAR occurring during the trial is compiled by the sponsor and sent to the principal investigators at all participating sites.

9.4 Follow-up of Adverse Events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.5 Independent Data Monitoring Committee

As the study is not randomized low intervention study a formal safety committee will not be appointed.

9.6 Annual Safety Report (ASR)

Since the sponsor is non-commercial and the marketing authorization holder of the investigational medicinal product is within the EU/EEA the SPC is used as RSI. The simplified template of Annual Safety Report will be used for the ASR reporting.

9.7 Procedures in case of emergencies, overdose or pregnancy

Medication errors, pregnancy and use of other medicinal products than those specified in the protocol, including misuse and abuse of the investigational medicinal product, shall be subject to the same reporting obligations as adverse reactions.

If an unforeseen event is likely to have a serious impact on the benefit/risk relationship of the trial, the sponsor and investigator should take appropriate Urgent Safety Measures (USM) necessary to protect the subjects. Examples of such measures are to temporarily halt the clinical trial or to introduce supplementary monitoring measures. The sponsor should, via CTIS, inform the concerned Member States about the event and the measures taken. Notification must be made as soon as possible, but no later than seven days after the measures have been taken.

If a subject or partner to a subject who participates in a clinical trial, becomes pregnant, this person will be followed up until the birth has taken place. If the foetus/child has any congenital malformation, this must be reported as a serious adverse event (SAE).

10 STATISTICS

10.1 Analysis population and statistical analyses including sample size calculations

A statistical analysis plan will be developed for the primary endpoint before start of inclusion and for all secondary endpoints before analysis. Descriptive statistical methods will be used to present data, and assuming a non-normally distributed data non-parametric statistics will be used.

Using a sample size of 82, the critical number of successes is 49. If 49 or more patients achieving complete response at one year, the null hypothesis will be rejected at alpha 0.05. Conversely, if 34 or more patients have negative response, then the null hypothesis cannot be rejected. If at any time 49 complete responses or 34 negative responses are observed, rejection/failure to reject is known with 100% certainty. However, we plan to include patients until the randomized controlled trial STAR-TREC continues follow-up.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Quality Assurance and Sponsor oversight

The sponsor's quality-related work is based on a risk analysis of the trial as a whole: design, conduct, data collection, evaluation, reporting and archiving. The sponsor will perform quality assurance and quality control activities for the trial; however, responsibility for the accuracy, completeness, and reliability of the trial data presented to the sponsor lies with the PI (and delegate(s)) generating the data.

11.2 Monitoring

The trial will be monitored by an independent monitor before the trial begins, during the conduct of the trial, and after the trial has been completed. This is to ensure that the trial is carried out according to the protocol and that data is reliably and robust and are collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring will be risk-based, which means that the extent of the monitoring is based on the sponsor`s risk-assessment and is performed as per the trial's monitoring plan, The monitoring is intended to ensure that the subject's rights, safety, and well-being are met and that data in the CRF are complete, correct, and consistent with the source data.

11.3 Source data

The investigator must keep source documents for each subject in the trial. A document describing what has been classified as source data in the trial (source data reference document) should be included in the Investigator Site File (ISF). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities.

Source data is defined before trial start at each individual site and can, in cases where source data is not registered in another document, consist of the CRF. This should be decided in consultation with the monitor and clearly stated in the source data reference document.

Access to trial-related documentation, such as subjects' medical records, data acquisition tools (DATs) (including CRFs), other source data and other trial documentation will be provided for monitoring and auditing purposes. Access to subjects' medical records will require a confidentiality agreement to be signed by the person in charge of the medical records at the trial site and by the monitor and auditor, if applicable. Access will also be granted in the context of regulatory inspections.

11.4 Deviations, serious breaches and other reporting obligations

The responsible investigator and/or any involved service provider shall, without delay, report to the sponsor any suspected serious breaches from the trial protocol, the CTR, ICH-GCP and other regulations that are likely to affect the safety, rights of the subjects and/or the data reliability and robustness to a significant degree. The sponsor should assess the suspected serious breach, the consequences of the deviations and without undue delay, but no later than 7 days (from knowledge), report these to the Competent Authorities via CTIS.

Other unexpected events that may affect the benefit/risk relationship for the clinical trial must be reported via CTIS without undue delay, but no later than 15 days after the sponsor becomes aware of the event.

Minor deviations that do not affect subjects’ integrity or safety, nor significantly affect the trial’s scientific value, are documented in the trial documentation of the principal investigator and the sponsor and appropriate measures shall be taken. The deviations, including minor deviations, must be recorded in the clinical trial report.

11.5 Audits and inspections

The purpose of an audit or inspection is to review trial-related activities and documents systematically and independently, to determine whether these activities were performed, registered, analysed and reported correctly according to the protocol, ICH-GCP and applicable regulations.

Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the trial site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections.

12 ETHICS

12.1 Compliance to the protocol, ICH-GCP and regulations

The trial will be performed in compliance with this clinical trial protocol, the EU regulation on clinical trials on medicinal products for human use (536/2014), the Declaration of Helsinki, ICH-GCP (Good Clinical Practice), and current national regulations governing this clinical trial. This is to ensure the safety and integrity of the trial subjects as well as the quality of the data collected

12.2 Ethical review of the trial

The final protocol for clinical trials on medicinal products must be approved, as a part of the application for a permit for clinical trials via CTIS, by the Competent Authorities, before the trial can be conducted. The authorities must be informed via CTIS of any changes in the trial protocol in accordance with current requirements.

12.3 Procedure for obtaining informed consent

The principal investigator at each site shall ensure that the subject is given full and adequate oral and written information about the trial, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the trial at any time without having to provide a reason. Subjects should be given the opportunity to ask questions and be allowed time to consider the provided information. If the subject chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as the informed consent form shall be provided to the subject. The subject's signed and dated informed consent must be obtained before any trial-specific activity is performed. Each subject who participates in the trial will be identified by a subject number on a subject identification list. The subject agrees that monitors, auditors, and inspectors may have access to the subject's medical records and other source data. If new information is added to the trial, the subject has the right to reconsider whether he/she will continue their participation.

12.4 Data protection

In the information provided to subjects, subjects will be fully informed about how their trial data will be collected, used and disclosed. The content of the informed consent form complies with relevant integrity and data protection legislation. The subject information and the informed consent form will explain how trial data are stored to maintain confidentiality in accordance with national data legislation. All information processed by the sponsor will be pseudonymized only identifiable with the study id.

The informed consent form will also explain that for verification of the data, representatives delegated by the sponsor, as well as relevant authorities, may require access to parts of medical records or trial records that are relevant to the trial, including the subject's medical history.

12.5 Insurances

All subjects participating in the trial are covered by the Swedish Patient Insurance (patientförsäkringen) through Regionernas Ömsesidiga Försäkringsbolag, LÖF.

13 SUBSTANTIAL CHANGES TO THE STUDY

Substantial changes to the signed clinical trial protocol are only possible through approved protocol amendments.

In the event that substantial changes to the protocol which may affect the safety, rights of subjects or the reliability and robustness of data generated need to be implemented during the course of the trial, permission from the relevant authority via application in CTIS should be obtained before implementing the change. This includes the addition of a new trial site or a change of the principal investigator at the trial site.

Non-substantial amendments are entered into the CTIS in the next substantial amendment application concerning the same part. If the non-substantial change is relevant to the Authority's oversight (e.g. contact details), the CTIS should be updated on an ongoing basis.

14 COLLECTION, HANDLING AND ARCHIVING OF DATA

14.1 Case Report Form - eCRF

The REDCap system will be used as electronic clinical record form (CRF) (https://www.project-redcap.org/). All data is kept within Region Västra Götalands firewall. Two-factor authentication is used, and data is securely stored according to rules and regulations for class III data. Data will be entered prospectively unless the patient is included after completed neoadjuvant treatment, when data up to that visit will be entered retrospectively. Data will be entered at the following time points and details on required information is presented in Table 1. Details on data entered in the CRF is presented in appendix.

14.2 Data collection

All clinical data at inclusion, during and after neoadjuvant treatment, during surgery, during postoperative hospital stay and at yearly follow-ups will be entered into the REDCap CRF. At inclusion the study centre at SSORG, Sahlgrenska University Hospital will receive a phone call and register the patient to ascertain that all patients are registered properly.

After this all registration will be performed using a study number, not the personal identification number. The personal identification number and the study number will be kept either in a locked storage or at in a password protected and secure SharePoint document.

The postoperative questionnaires will be administered by the study secretariat at SSORG.

All data will be kept within University of Gothenburg and Sahlgrenska University Hospital IT systems using inherent security systems.

A logistic database with complete patient ID will be used, kept within a separate IT-system from the result database with all study information. Security measures will include one to maximum two users of this database, with unique usernames and personal login, as well as automatic throw-out.

The result database, based on trial number and without patient ID, will be kept within another IT system than the logistic database. The database will be kept on a server with automatic backup and will be registered with “integritetsskyddsombudet” for Sahlgrenska University Hospital.

14.3 Data management plan

A data management plan (DMP) based on the Swedish National Data Service (SND) checklist has been drawn up and will be continuously revised during the project. The plan covers all handling of data from project planning, through collection, analysis, and archiving.

The project has a designated data manager who work with storing and validating of data in the project. To uphold data security and integrity of study participants the routines of Västra Götaland Region and University of Gothenburg guidelines for handling sensitive data are followed.

Data in this project will contain information concerning health and is thereby classified as sensitive personal data by General Data Protection Regulation (GDPR). The processing of the

sensitive data for scientific research purposes in this project will be according to GDPR article 9 with lawful basis of public interest article 6e. The organisations that act as data controller for this project is Sahlgrenska University Hospital and University of Gothenburg.

Confidentiality is identified as grade III and will thereby be protected by strong authentication when stored and encryption when transferred.

Integrity is identified as grade III and will be protected against unintentional and unauthorised alteration. Routines for data to be regularly backed up as well as logging of alteration will be in place.

Availability is identified as grade II and should be accessible at most hours and is established by stable and well tested IT-infrastructure.

All data is pseudonymised and the key is stored in a separate secure server system not containing any study data.

Clinical data will be entered directly in an electronic clinical record (CRF) by each participating centre through the REDCap web interface (https://www.project-redcap.org/). Data collected via REDCap will be stored directly on a server within the Västra Götaland Region firewall and is accessed through a two-factor authentication. Data can be accessed and retrieved from the data base only with the authorization by the principal investigator.

Patient-reported outcomes will be retrieved by questionnaires. The study secretariate has well built-up infrastructure as well as experiences of handling sensitive and confidential data from randomised clinical trials. The logistics database with contact information on study participants is password protected. Accesses is given only to personnel who work in direct contact with participants for retrieving questionnaire during the study follow up period.

Radiological and radiotherapy data will be analysed, stored, and processed according to regulation. The infrastructure used will either be within the Sahlgrenska University Hospital or by an external infrastructure explicitly for research purpose. In the latter case a data processor agreement will be established.

Blood samples and biopsies will be marked only with study code and stored in biobank according to regulation. Data for the translation sub study will be analysed, stored, and processed according to the routines and infrastructure at Core Facilities at Sahlgrenska Academy, University of Gothenburg.

Access to data will be given only for those who will actively work with data. Access to data for researchers and statisticians will be restricted to the data need for each analysis. Data manger will have access to all data retrieved by the study secretariate, as well as data in each analysis used for publication. Only the principal investigator group will have full access to all collected data in the project.

If any data is to be processed outside of the data controller organisations a data processor agreement will be established to ensure that GDPR is followed.

Any physical data containing personal information (e.g. paper questionnaires, consent forms) will be stored in locked rooms in buildings accessed only by authorised personal within the Sahlgrenska University Hospital.

All participants will be informed on how data are managed and their rights according to GDPR before entering the study.

15 NOTIFICATIONS OF TRIAL COMPLETION, REPORTING AND PUBLICATION

End of recruitment of subjects and end of the trial is reported in CTIS, within 15 days. Within one year of trial completion a summary of the clinical trial results must be reported in CTIS, including a summary for lay people. In addition, a full clinical trial report with individual data is to be completed and archived in the trial master file by sponsor and in the investigator-site files at each site.

The trial will be published after completion of the inclusion and completion of follow-up of patients with respect to results regarding the primary and secondary endpoints. As this is a prospective cohort study without randomization short term results may be published before the primary endpoint has been reached.

The principal investigators will be first author and/or last authors of main papers based on this study. Members of the writing committee qualify for co-authorship and will be determined according to section 1.4. The others qualify for acknowledgements.

In case of papers of side results authors have to be appointed by the writing committee based on the topic studied and investigators involved.

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17. APPENDIX

Appendix A – Frågeformulär

Appendix B – Variabellista

Appendix C – Flow chart