

**Can we Save the rectum by watchful waiting or TransAnal microsurgery following
(chemo)Radiotherapy versus Total mesorectal excision for early Rectal Cancer? – STAR-
TREC study: Protocol for a multi-centre, randomised feasibility study**

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Abstract:

INTRODUCTION: Total mesorectal excision is the highly effective standard treatment for rectal cancer but is associated with significant morbidity and may be over-treatment for low risk cancers. This study is designed to determine the feasibility of international recruitment in a study comparing organ saving approaches versus standard TME surgery.

METHODS AND ANALYSIS: The STAR-TREC trial is a multicentre international randomised, 3 arm-parallel, phase II feasibility study in patients with biopsy proven adenocarcinoma of the rectum. The trial is coordinated from Birmingham UK with national hubs in Radboudumc (The Netherlands) and OUH Svendborg UMC (Denmark). Patients with rectal cancer, staged by CT and MRI as \leq cT3b (up to 5mm of extramural spread) N0M0 can be included. Patients will be randomised to either standard TME surgery (control), organ saving treatment using long course concurrent chemoradiation, or organ saving treatment using short course radiotherapy. For patients treated with an organ saving strategy, clinical response to (chemo)radiotherapy determines the next treatment step. An active surveillance regime will be performed in the case of a complete clinical regression. In the case of incomplete clinical regression, patients will proceed to local excision using an optimized platform such as transanal endoscopic microsurgery (TEM) or other transanal techniques (e.g. TEO, TAMIS). The primary endpoint of this phase II study is to demonstrate sufficient international recruitment in order to sustain a phase III study incorporating pelvic failure as the primary endpoint. Success in phase II is defined as randomisation of at least 4 cases per month internationally in year 1, rising to at least 6 cases per month internationally during year 2.

ETHICS AND DISSEMINATION: The medical ethical committees of all the participating countries have approved the study protocol. Results of the primary and secondary endpoints

will be submitted for publication in peer-reviewed journals.

TRIAL REGISTRATION: ISRCTN14240288, ISRCTN registry, 20/10/2016; and NCT02945566, clinicaltrials.gov, oct/2016.

Strengths and limitations of this study

- This phase II study is the first study to randomise between the standard of care in early rectal cancer (i.e. TME surgery) and two organ saving strategies using (chemo) radiotherapy followed by selective transanal microsurgery.
- The STAR TREC study will show whether it is feasible to recruit enough patients for a consecutive international large, multi-centre randomised phase III trial.
- The study design incorporates several adjustments in standard (chemo)radiation therapy protocols intended to reduce treatment related side effects associated with organ saving therapy.
- Clinical nodal staging of rectal cancer is rather unreliable and patients with false negative nodal disease will be included in the study.
- Experience with clinical judgement of a complete response is difficult and needs to be monitored carefully with central reviewing during the study.

Introduction

The introduction of bowel cancer screening is associated with a significant increase in the incidence of early stage rectal cancer [1, 2]. Total Mesorectal Excision (TME) surgery is an effective oncological treatment for early stage rectal cancer, only 2% and 12% of patients experience local or distant failure respectively [3-5]. However, standard surgery for rectal cancer requires permanent stoma formation in 10-20% of cases and temporary stoma formation in 60-70% [6, 7]. Many temporary stomas are not reversed [8, 9]. Furthermore, TME surgery is associated with major morbidity and mortality in a significant number of patients. Over 50% of all patients following TME surgery experience faecal incontinence, whereas urinary problems and sexual dysfunction are observed in 32-80% of patients [10-14]. Another complication following TME surgery is anastomotic bowel leakage which occurs in approximately 15% of patients [15]. In addition, quality of life studies show that TME surgery is associated with persistently poor social role and body image [12, 16-19]. Mortality following TME surgery rises with age; the six-month mortality following TME surgery is 2.0-4.6 % for young rectal cancer patients and 9.0-13.4% for elderly patients (aged >75 years) [20-22]. There are concerns that TME surgery, which evolved to treat locally advanced, symptomatic tumours, may result in significant over-treatment of early screen-detected tumours. An organ preserving strategy may generate significantly less morbidity without substantially compromising oncological outcomes. Promising outcomes have been reported for (chemo)radiation therapy followed by watchful waiting or local excision.

Habr-Gama's group have notably published a watchful waiting approach to rectal cancer. Of 265 predominantly T3 rectal cancer patients treated with chemoradiotherapy (CRT), 71 patients (27%) had a complete clinical response (cCR) [23, 24]. These patients did not have

surgery and after a mean follow up of 57 months (range 18-156) only two patients developed local recurrence, one of which was successfully salvaged. A Dutch group then prospectively selected patients with cCR for a watchful waiting strategy (N=21) [25]. After a mean follow-up 25 months (\pm 19 months), one patient had developed a local recurrence which was salvaged by surgery and all other patients were alive without disease. In 2015, the effect of a radiation boost after CRT was evaluated in a prospective observational Danish study. A watch and wait policy was possible in 40 out of 51 included patients [26]. At one year, local recurrence occurred in 16% of 40 patients who initially showed a cCR. Rectal bleeding was relatively frequent in this study during follow-up perhaps relating to the higher radiotherapy doses that were used. However, these results which combine high cCR rates and low local recurrence rates have not been consistently replicated [27, 28]. Furthermore, CRT is associated with treatment-related morbidity and a mortality-rate of 0.5-1% should be considered [29].

Another organ saving treatment strategy is local excision instead of radical surgery. Early rectal tumours may be locally excised through the anus with low morbidity and mortality using Transanal Endoscopic Microsurgery (TEM), allowing rectal saving treatment [30, 31]. Morbidity and mortality after local excision are much lower than after major resection. Morbidity associated with TEM includes bowel perforation, (transitory) incontinence, wound infection and local pain [32-34]. In a study of 5,305 patients with early-stage rectal cancer, 30-day mortality after local excision was found to be 0.5% compared with 2.4% in patients undergoing major resection ($P = 0.008$). Morbidity within 30 days of surgery was 4.4% in the local excision group versus 12.7% in the major resection group ($P < 0.001$) [34]. However, the risk of non-radical resection after local excision is higher and the risks of leaving behind

microscopic lymph node metastases, is a potential cause of local failure [5, 35]. 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 [36].

Combining radiotherapy with TEM surgery could possibly lead to better outcomes because radiotherapy can effectively treat microscopic mesorectal nodal metastases and contribute to tumour downsizing [37, 38]. However, limited prospective evidence currently exists to guide the use of radiotherapy and local excision as curative treatment for early rectal cancer. Lezoche et al randomised 100 patients with T2N0 rectal cancer to chemoradiation therapy (CRT) followed by laparoscopic TME surgery or chemoradiotherapy and TEM with a 6-8 week interval to surgery [39]. After a median follow-up of nine years, local recurrence rates were 6% and 8% in the TME and TEM arms respectively. In a trial of 89 patients with unfavourable cT1N0, cT2N0 or borderline cT2/3N0 tumours by Bujko et al, patients were given neoadjuvant treatment with short course radiation therapy (SCRT) or CRT prior to delayed local excision [40]. No further treatment was offered for good responders, whereas immediate TME surgery was recommended for all other patients. Good responders had a 2-year local recurrence rate of 10%. Of the poor responders, eight patients had a TME and none of this group had a recurrence, however, 18 declined or were unfit for TME, and this group had a 2-year local recurrence rate of 37%. This underlines that in high-risk or poor responding patients, neoadjuvant radiotherapy followed by local excision is inadequate treatment.

CARTS was a non-randomised phase II study that evaluated CRT followed by TEM in 55 patients with stage T1-3N0 rectal cancer [41]. Clinical response was assessed 6-8 weeks after completion of CRT and TEM was performed. Organ saving was achieved in more than half of

patients and 21 had ypT0 disease. Radiotherapy consisted of 50Gy in 25 fractions and capecitabine 825mg/m² bid was given for the same period 7 days per week. However, 42% of patients developed at least grade 3 toxicity and there were two toxicity related deaths. A multicenter cohort study from the UK that employed SCRT with TEM after ten weeks demonstrated that 43/62 cases had either no or minimal residual disease following radiotherapy [42]. None of these patients experienced short term pelvic relapse and treatment related toxicity was low. The ACOSOG Z6041 study, a single arm phase II study, evaluated an oxaliplatin and capecitabine concurrent chemotherapy schedule combined with 54Gy of pelvic radiotherapy followed by TEM for T2N0 rectal cancer [43]. Both radiotherapy and chemotherapy schedules required reduction during the study due to acute toxicity. Only 3 out of 79 evaluable patients experienced local failure as first event. TREC is a phase II UK study evaluating the feasibility of randomising patients to receive either organ saving treatment with SCRT and TEM versus standard TME surgery. This study is due to report in 2017 having completed minimum 2 year follow up.

In conclusion, several strategies can be followed to improve the quality of life of rectal cancer patients by aiming for organ preservation. However, all data so far are derived from small phase II studies and many questions regarding the optimal radiotherapy schedule and the optimal timing of evaluation remain. In addition, prospective comparative data with radical surgery are not available. Therefore, there is an urgent need for a randomised phase III trial to establish the risks, complication rates and benefits of organ saving compared to standard radical surgery for early stage rectal cancer. The aim of the STAR-TREC study is to assess the feasibility of successfully recruiting to a large, multi-centre randomised trial

comparing radical surgery versus organ saving treatment using (chemo) radiotherapy followed by selective transanal microsurgery.

Methods and analysis

Design

The STAR-TREC trial is a multicentre international randomised, 3 arm-parallel CTIMP study in patients with biopsy proven adenocarcinoma of the rectum. The trial is coordinated from Birmingham UK with national hubs in Radboudumc (The Netherlands) and OUH Svendborg UMC (Denmark). Participants are currently being recruited and enrolled; the first patient was enrolled in July 2017.

The primary endpoints of the STAR TREC study (phase II) are defined as:

1. Year 1: Randomise at least 4 cases per month internationally (n=48);
2. Year 2: Randomise at least 6 cases per month internationally (n=72).

The secondary endpoints of this phase II trial are:

1. Year 1: Can one international partner procure independent funding in year 1? Successful international collaboration will be necessary to deliver a future phase III study.
2. Year 1: Can one international partner open the study to recruit in year 1?
3. Efficacy of organ preserving treatment arms on completion of phase II study: Is the organ saving rate >50% at 12 months (following randomisation) in the experimental arms?

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

Safety

- Accuracy of MRI in predicting STAR-TREC eligibility
- 30-day and 6 month mortality
- Surgical morbidity
- Rate of tumour recurrence or regrowth within the bowel wall (experimental arm)
- Rate of tumour recurrence within the mesorectum (experimental arm)
- Rate of distant metastases
- Pelvic failure rate: expressed as a sum of the following (i) unresectable pelvic tumour, (ii) cases requiring beyond TME surgery or (iii) tumour recurrence or regrowth ≤ 1 mm from the circumferential surgical margin after TME surgery. This outcome measure will be pivotal in challenging current clinical practice and it is our intention that it becomes the primary endpoint in phase III.
- Bowel, bladder and sexual dysfunction (baseline and 12, 24 months post randomisation)

Efficacy

- Proportion of patients with/ without a stoma at 30 days and one year

- Histopathological assessment of tumour down-staging following radiotherapy according to depth of tumour invasion and the incidence of other high-risk features in comparison to non-irradiated (control) group.
- Proportion of patients identified by clinical and MRI assessment as suitable for active monitoring
- Conversion rates from organ saving to radical surgery
- Disease free survival
- Quality of life (baseline and 12, 24 months post randomisation)
- Overall survival

Study population

This is a hospital-based study. Centre eligibility depends on a radiotherapy trials quality assurance (RTTQA) which is a mixture of an approved departmental standard operating procedure and successful contouring of a case using the new principles of mesorectal irradiation. Candidates will generally be identified in the endoscopy suite following referral for (i) the investigation of new bowel symptoms, (ii) as part of a personal bowel surveillance programme or (iii) through national bowel screening. Subjects will then be referred on to either a colorectal surgeon or the colorectal cancer multidisciplinary team (MDT) meeting. Eligibility will be confirmed at the MDT meeting. The main in- and exclusion criteria for the trial are summarized in Table 1.

Study arms

Patients will be randomised to either standard TME surgery (control), organ saving treatment using long course concurrent CRT or organ saving treatment using SCRT (Figure 1). Patients allocated to TME surgery will have a minimum of one abdominal Computed Tomography (CT) scan and regular clinical follow-up will be made according to national guidelines. In the two organ saving arms, response assessment will take place at 11-13 weeks from the start of (chemo)radiotherapy and again at 16-20 weeks from start. Initial assessment at 11-13 weeks (MRI and endoscopy) will identify a small proportion of cases where radiotherapy has had little or no impact upon tumour dimensions. Non-responding patients will be advised to convert to standard TME surgery. Individuals whose tumours demonstrate a satisfactory response at this time point will be examined once again at 16-20 weeks (endoscopy) to determine if a cCR has occurred. It is anticipated that this interval between assessments will allow for additional tumour regression and resolution of acute radiotherapy reactions, facilitating more precise diagnosis of cCR. An active surveillance regime will be performed in the case of a cCR. In the case of incomplete clinical regression, patients will progress to local excision, see figure 1. Representative endoscopic images will be centrally reviewed during this feasibility stage to develop a consistent approach to interpretation of the clinical assessment.

All patients must be assigned to one of the three treatment groups by week 20:

- (1) Poor response assessed at 11-13 weeks – patient recommended to convert to radical TME surgery.
- (2) Clinical complete response (cCR) assessed at 16-20 weeks means that the bowel wall has reverted to normal and patients are treated by watchful waiting.

(3) Clinically satisfactory, yet incomplete tumour response at 16-20 weeks, meaning a 50% or more reduction of tumour size and the presence of any residual mucosal or bowel wall abnormality suggestive of persisting tumour, will prompt local excision by TEM.

Treatment regimen for organ saving strategies

Long course CRT consists of capecitabine and is administered at a dose of 825 mg/m² bid on radiotherapy days only. A total dose of 50 Gy will be applied to the primary tumour and surrounding mesorectum, in 25 fractions of 2 Gy, 5 days per week.

SCRT consists of a total dose of 25 Gy, applied to the primary tumour and surrounding mesorectum in 5 fractions of 5 Gy, preferably on 5 consecutive days. Radiotherapy for organ preservation is primarily aimed at tumour downstaging and can therefore be restricted to the peritumoural area including the primary tumour and the mesorectum resulting in a significant reduction in the irradiated target volume.

Randomisation

Patients will be randomised on a 1:1:1 basis between standard surgical treatment and organ saving treatments. Randomisation will be provided by a computer-generated program at the University of Birmingham Clinical Trials Units (BCTU). The randomisation programme will use a minimisation procedure for the following variables:

1. MRI Tumour staging (\leq T3a N0 V0 and T3b N0 V0)

T3a: tumour extends <1 mm beyond muscularis propria

T3b: tumour extends 1-5 mm beyond muscularis propria

2. Country (UK, the Netherlands, Denmark)

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

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

Sample size

No power calculation is provided as the primary objective is to show feasibility of recruitment. The aim of the present trial is to include 4-6 patients per month in order to have a high enough randomisation rate to perform a phase III trial. For a phase III trial the primary outcome would be 3-year pelvic failure. The null hypothesis is that the increase in the rate of pelvic failure at 3 years with organ preservation compared to standard surgery is less than 7% absolute difference. Prior data indicate that the pelvic recurrence rate in the radical TME group is 2%. If the true recurrence rate for patients in an experimental arm is 9% then, using 90% power and $\alpha=0.025$ (to account for two treatment comparisons) would require 117 patients per treatment arm. Anticipating a 10% dropout rate, we would aim to randomise 400 participants. The final decision for a phase III sample size will be taken from information gained during the feasibility study. Data of the phase II trial will be used for the phase III trial.

Data management

Case report forms (CRF) can be entered online at <http://www.bctu.bham.ac.uk/STAR-TREC>.

Authorised staff at sites will require an individual secure login username and password to access this online data entry system. Paper CRFs must be completed, signed/dated and returned to the National STAR-TREC Trial Office by the Investigator or an authorised member of the site research team. Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All missing and ambiguous data will be queried. All sections are to be completed.

Assessment of the health related quality of life will be done after the patients have completed a series of questionnaires. The questionnaires EORTC QLQ C30 and CR29, EQ-5D, LARS score and ICIQ-MLUTS/ ICIQ-FLUTS will be done at three time points, at baseline prior to treatment and at follow-up 12 and 24 months after the start of treatment.

All trial records must be archived and securely retained for at least 25 years. No documents will be destroyed without prior approval from the Sponsor, via the Central STAR-TREC Trial Office. On-site monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan for each participating country. Any monitoring activities will be reported to the central STAR-TREC office and any issues noted will be followed up to resolution. STAR-TREC will also be centrally monitored; however additional on-site monitoring may occur if triggered. Further information regarding data management is provided in the study protocol.

Ethics and dissemination

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, and stated in the respective participating countries laws governing human research, and Good Clinical Practice. The medical ethical committees of all the participating countries have approved the study protocol.

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. Results of the primary and secondary endpoints will be submitted for publication in peer-reviewed journals.

Discussion

The TREC and CARTS groups have combined with colleagues in Denmark to design the STAR-TREC study. Phase II data from TREC and CARTS justifies a randomised comparison of standard radical surgery versus organ saving treatment using either SCRT or CRT with selective use of transanal microsurgery based upon a radiotherapy response assessment. Organ preservation is not standard treatment and testing the feasibility is important to determine the scale of randomised trial that can be performed. The phase II STAR-TREC study will evaluate the feasibility of accelerating recruitment to an international three arm randomised trial.

The published literature supports use of (chemo)radiotherapy and transanal microsurgery as an alternative to major surgery for curative treatment of early rectal cancer. To date, studies have recruited patients who were highly motivated to organ preserving treatment. Broader patient populations are yet to be evaluated using these organ saving treatments. In addition, the long term impact of organ saving treatment after neoadjuvant treatment, upon quality of life and, more importantly, oncological outcome is unknown. Therefore, these organ preserving strategies should ideally be compared to radical TME surgery which represents the current standard of care for patients with rectal cancer. A randomised trial comparing organ saving treatment with major surgery might be practice changing for the treatment of early rectal cancer patients.

In addition, while it seems probable that a strategy of organ saving may produce substantial benefits over conventional radical surgery, the optimum organ saving treatment schedule remains unclear. Phase II studies suggest that SCRT may have the lowest acute toxicity while

CRT may achieve the highest cCR rates. Randomisation between these two strategies with the interval calculated from the start of (chemo)radiotherapy will give insight in the possible difference in efficacy in these early cancers. STAR-TREC is therefore an international, multi-centre, randomised, phase II feasibility study comprising a 1:1:1 randomisation for eligible subjects with early clinically localized rectal cancer.

While published data supports further evaluation of organ saving in patients with early stage rectal cancer utilizing either SCRT or CRT followed by transanal microsurgery, it has also become clear that not all patients require surgery. Watchful waiting after complete response is being investigated in patients already in need of CRT [24, 26, 37]. Other studies introduce (chemo)radiation therapy to the treatment regimen in order to facilitate organ preservation. Current techniques utilise either SCRT (5 fractions of 5 Gy) [40, 42] or concurrent fluoropyridine based CRT (25 fractions of 1.8 or 2 Gy) [38-40, 42]. Radiotherapy is routinely followed by TEM, to remove the portion of bowel wall affected by cancer. However, in a significant proportion of patients, there are no signs of residual tumour following radiotherapy. This is termed a cCR. These patients are likely over-treated by routine transanal microsurgery and therefore possibly subjected to unnecessary surgery related morbidity. Therefore, patients with a cCR might be better served by a watchful waiting approach [44].

The STAR-TREC study design incorporates several developmental steps, each intended to further reduce treatment related side effects associated with organ preserving therapy:

1. Modification in the capecitabine dose from 825mg/m² bid 7 days per week used in CARTS to 825 mg/m² bid 5 days per week.

2. Use of a smaller radiotherapy volume incorporating only the primary tumour, rectal wall and mesorectum.
3. Use of a two-step clinical response assessment tool following (chemo)radiation so that (i) poor responders are converted to radical TME surgery at the earliest opportunity while (ii) good responders are given more time to determine if they reach complete clinical response and may avoid transanal microsurgery.
4. Selective use of transanal microsurgery/TEM for residual mucosal or bowel wall abnormality suggestive of persisting cancer.
5. Objective comparison of the efficacy of CRT versus SCRT with similar intervals between start of radiotherapy and evaluation.

To date, no significant differences are considered for target volume definition for early or advanced rectal cancers. Target volumes contain at least the primary tumour, the mesorectal fat, presacral and internal iliac nodes [45]. Given that patients in STAR-TREC will be clinically node negative, the necessity of irradiating presacral and iliac nodes is questionable. Even in the case of unexpected nodal involvement, the majority of involved lymphnodes will be peritumoural in the mesorectum, as demonstrated in a series of 121 patients with locally advanced rectal cancer who underwent chemoradiotherapy [46]. The radiotherapy volume has therefore been reduced to the mesorectal fat only. To ensure safe introduction of this new technique, strict radiotherapy quality assurance is part of the protocol.

STAR-TREC is designed to achieve a recruitment rate that would provide confidence that extension into a phase III trial is achievable. Further applications for funding, ethics approval and a substantial protocol amendment would be required for this transition.

Conclusion

There is an urgent need for a randomised phase III trial to establish the risks and benefits of organ saving compared to standard TME surgery for early stage rectal cancer. The STAR-TREC trial builds on experience gained through the TREC and CARTS phase II studies. STAR-TREC is a multicenter international randomised phase II study designed to assess the feasibility of recruiting 6 international patients per month in order to facilitate the evaluation of TME surgery versus organ saving strategy preceded by (chemo)radiation in two different fractionation schedules. The trial aims to improve the rate of patient recruitment compared to earlier studies and will also introduce a mesorectal target volume with quality assurance. The ultimate goal of this phase II feasibility study is to accelerate to a phase III study comparing TME surgery with two organ saving treatment regimens.

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List of abbreviations

BCTU - Birmingham Clinical Trials Units; **bid** – twice daily; **CARTS** – Trial: Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery; **cCR** - complete clinical response; **CRT** - Chemo Radiation Therapy; **CT** - Computed Tomography; **CTIMP** - Clinical Trial of an Investigational Medicinal Product; **EORTC QLQ CR 29&C30** – European Organisation for Research and Treatment of Cancer Quality of life questionnaires for colorectal cancer; **ERUS** – EndoRectal UltraSound; **ESMO** – European Society for Medical Oncology; **EQ-5D** – standardised questionnaire for use as a measure of health outcome; **Gy** - Grey; **HRQL** – Health Related Quality of Life; **ICIQ-MLUTS** - Patient-completed questionnaire for evaluating male lower urinary tract symptoms and impact on quality of life; **ICIQ-FLUTS** - Patient-completed questionnaire for evaluating female lower urinary tract symptoms and impact on quality of life; **LARS score** – Low Anterior Resection Syndrome score; **MDT** - Multi Disciplinary Team meeting; **MRI** - Magnetic Resonance Image; **MRIemvi** - MRI extramural vascular invasion; **MRItrg** - MRI based tumour regression grade; **RTTQA** - RadioTherapy Trials Quality Assurance; **SCRT** - Short Course Radiation Therapy; **STAR-TREC** - Trial name – Can we Save the rectum by watchful waiting or TransAnal microsurgery following (chemo)Radiotherapy versus Total mesorectal excision for early Rectal Cancer; **TAMIS** – TransAnal Minimally Invasive Surgery; **TEM** - Trans anal Endoscopic Microsurgery; **TEO** – Transanal Endoscopic Operation; **TME** - Total Mesorectal Excision; **TMG** – Trial Management Group; **TREC** – Trial: Transanal endoscopic microsurgery and radiotherapy in early rectal cancer; **UK** – United Kingdom.

Authors' contributions

All collaborators made substantial contributions to the design of the study and/or were involved in drafting the manuscript. All collaborators read and approved the final manuscript.

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Competing interests statement

There are no competing interests to declare.

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Table 1 – Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age >16 years (UK), Age >18 years (Netherlands and Denmark)	1. MRI node positive*
2. Biopsy proven adenocarcinoma of the rectum	2. MRI extramural invasion (mriEMVI) present*
3. Magnetic Resonance Image T1-3b N0 M0 rectal tumour	3. MRI defined mucinous tumour
4. Multi disciplinary team meeting determines that the following treatment options are all reasonable and feasible: (a) TME surgery, (b) Chemo Radiation Therapy, (c) Short Course Chemo Radiation Therapy (d) TEM	4. Mesorectal fascia threatened by tumour ($\leq 1\text{mm}$ on MRI)
5. Estimated creatinine clearance >50 ml/min	5. Maximum tumour diameter > 40mm; measured from everted edges on sagittal MRI
	6. Anterior tumour location above the peritoneal reflection on MRI or ERUS
	7. No residual luminal tumour following endoscopic mucosal resection
	8. Prior pelvic radiotherapy
	9. Regional or distant metastases

* Defined by protocol guidelines