TREC TRIAL PROTOCOL

Transanal Endoscopic Microsurgery (TEM) and Radiotherapy in Early Rectal Cancer

A randomised Phase II feasibility study to compare radical TME surgery versus short course preoperative radiotherapy with delayed local excision for treatment of early rectal cancer.

Developed by the National Cancer Research Institute (NCRI) Colorectal Clinical Studies Group and funded by Cancer Research UK.

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TREC Trial Management Group

**Surgery**
Mr Simon Bach (Chief Investigator)
University Hospital, Birmingham
simon.bach@uhb.nhs.uk

Professor Dion Morton
University Hospital Birmingham
dion.morton@uhb.nhs.uk

Professor John Monson
University of Rochester, New York
john.monson@urmc.rochester.edu

Professor Neil Mortensen
John Radcliffe Hospital, Oxford
neil.mortensen@nds.ox.ac.uk

Mr James Hill
Manchester Royal Infirmary
james.hill@cmmc.nhs.uk

Mr Chris Cunningham
John Radcliffe Hospital, Oxford
chriscunningham.ogi@gmail.com

Mr Stephan Korsgen
Good Hope Hospital, Sutton Coldfield
stephan.korsgen@heartofengland.nhs.uk

**Pathology**
Professor Phillip Quirke
St James’s University Hospital, Leeds
philip.quirke@leedsth.nhs.uk

**Radiology**
Dr Gina Brown
The Royal Mardensen Hospital
gina.brown@rmh.nhs.uk

**Radiotherapy**
Dr Ian Geh
University Hospital, Birmingham
ian.geh@uhb.nhs.uk

Professor David Sebag-Montefiore
St James’s University Hospital, Leeds
d.sebag-montefiore@leeds.ac.uk

Dr Arthur Sun-Myint
Clatterbridge Hospital, Wirral
sun.myint@cccotrust.nhs.uk

Elizabeth Southgate
Heartlands Hospital, Birmingham
elizabeth.southgate@uhh.nhs.uk

**Trials Management**
Dr Laura Magill
Birmingham Clinical Trials Unit
e.l.magill@bham.ac.uk

**Medical Oncology**
Dr Pauline Leonard
The Whittington Hospital

**Patient Representative**
Ann Russell
ann@madasus2.co.uk

**Statistics**
Professor Richard Gray
University of Oxford, CTSU
richard.gray@ctsu.ox.ac.uk

Dr Kelly Handley
Birmingham Clinical Trials Unit
k.handley@bham.ac.uk

---

**Data Monitoring and Ethics Committee**

Chair: Professor Richard Peto
University of Oxford
secretary@ctsu.ox.ac.uk

Dr Tom Crosby
Velindre Hospital
tom.crosby@velindre-tr.wales.nhs.uk

Mr Brendan Moran
Basingstoke and North Hampshire Hospital
Brendan.Moran@hhft.nhs.uk

Dr Julie Olliff
Queen Elizabeth Hospital Birmingham
julie.olliff@uhb.nhs.uk
**TREC Study Office**

For general queries, supply of trial materials, and collection of data:

BCTU, Robert Aitken Institute, School of Cancer Sciences, University of Birmingham, B15 2TT

Tel: 0121 415 9100 (answering machine outside office hours); Fax: 0121 415 9135

| Trial Coordinator | Dr Laura Magill | 0121 415 9105 | e.l.magill@bham.ac.uk |
| Computing         | Nick Hilken    | 0121 415 9121 | n.h.hilken@bham.ac.uk |

**Randomisation**

Telephone: 0800 953 0274 (toll free in UK) or +44 (0)121 415 9137 (outside the UK)

Clinical Queries during office hours should be directed to one of the Clinical Co-ordinators or to an appropriate member of the Trial Management Group.

Other queries should be directed to the TREC Study Office.

**Trial Sponsor:** University of Birmingham, Edgbaston, Birmingham, B15 2TT; Tel: 0121 414 3898

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1. BACKGROUND

1.1. Increasing incidence of early rectal cancer poses new surgical dilemma
Introduction of the NHS Bowel Cancer Screening Program (NBCSP) is changing how rectal cancer presents. Pilot studies report that 49-62% of screen-detected cancers are ‘early’ (pT1-2N0M0; Stage I). While radical total mesorectal excision (TME) is a highly effective treatment for symptomatic rectal cancer, as only 3-6% of patients experience local relapse, mortality from the procedure is significant at 3-4% and post-operative morbidity substantial (see below). There are concerns, therefore, that radical surgery, which evolved to treat locally advanced, symptomatic tumours, may not be the optimal method of treatment for early screen-detected tumours. Local excision, with radical therapy salvage in the event of recurrence, could be safer and functionally far superior without substantially compromising cancer survival.

1.2. Benefits and risks of radical TME surgery
Radical TME surgery for early rectal cancer offers high rates of cure but is also associated with iatrogenic effects such as pain, infection, incontinence, impotence and occasionally death. Six-month mortality following radical curative surgery for rectal cancer is 4.6% for patients aged 65-74 years and 13.4% for patients aged 75-84 years according to Netherlands registry and RCT data collated since 1990. These findings are consistent with those of the Association of Coloproctology of GB&I audit. Treatment of elderly patients should perhaps focus more closely on preventing early non-cancer related deaths. The Dutch TME trial, reported clinical bowel leaks in 16% of non-irradiated patients. Pelvic dissection may inadvertently cause autonomic nerve damage leading to urinary incontinence or retention (25%-34%) and sexual dysfunction. More than half of all patients experience some form of faecal incontinence following TME surgery and 30-40% suffer daily symptoms of urgency, incomplete emptying and stool frequency. Three prospective cohort studies have examined health related quality of life scores following rectal cancer surgery. Each demonstrated persistently poor social, role, body image and defaecation scores. The question remains whether this level of surgical morbidity and mortality is necessary for the satisfactory treatment of early rectal cancer. An organ preserving local approach may generate significantly less morbidity without substantially compromising oncological outcomes.

1.3. Local excision alone for early rectal cancer
Early rectal tumours may be locally excised through the anus with low morbidity and mortality using Transanal Endoscopic Microsurgery (TEMS). Local disc excision of the primary tumour, plus an adequate margin of normal tissue, allows for preservation of the rectum. But, omitting total mesorectal excision risks leaving behind microscopic lymph node metastases, a...
potential cause of local failure. The probability of tumour spread to mesorectal nodes\textsuperscript{3,4,18} and the rate of local failure following TEMS\textsuperscript{16} can be estimated using predictive histopathological biomarkers in the locally excised specimen. ‘Low-risk’ lesions have recurrence rates of <5% and require no further treatment.\textsuperscript{16} The majority of cases, perhaps 75%, have an intermediate probability of local recurrence following TEMS (10-30%). Histopathological risk stratification lacks precision, though, and is unable to discriminate reliably between cases that have been effectively treated by local excision from those where conversion to radical TME surgery would be beneficial.\textsuperscript{16} Conversion of all intermediate risk patients to radical surgery would provide no additional benefit for the majority, although taking no further action would result in unacceptable levels of recurrence. Selective post-operative radiotherapy for ‘high-risk’ cases has failed to deliver satisfactory improvements in disease control.\textsuperscript{16,19} Pre-operative radiotherapy is more effective than post-operative radiotherapy\textsuperscript{20,21} and could reduce local recurrence after local excision to acceptable levels.

1.4. Pelvic radiotherapy

Efficacy of preoperative radiotherapy in combination with radical surgery

Four large RCTs, involving over 4000 rectal cancer patients from three countries, show that addition of preoperative radiotherapy to radical TME surgery reduces the incidence of local recurrence in both early and locally advanced disease.\textsuperscript{6,20-22} Preoperative radiotherapy can induce tumour shrinkage (downsizing/downstaging) or even a pathological complete response (pCR). Key to downstaging is an interval between completion of radiotherapy and surgery.\textsuperscript{23} ‘Long course’ chemoradiation is the established treatment for downstaging advanced rectal tumours that encroach upon the surgical margin according to pre-operative MRI. Alternatively, short course preoperative radiotherapy (SCPRT) is used to reduce the incidence of local recurrence where margins appear clear. Traditional schedules of SCPRT do not produce substantial downstaging as surgery follows immediately after the one-week course.\textsuperscript{24} However SCPRT may effectively downstage locally advanced tumours if surgery is delayed.\textsuperscript{25,26} This concept is being prospectively evaluated as part of the Stockholm III study.

Side effects of pelvic radiotherapy in combination with radical surgery

Direct comparison of neoadjuvant long and short course radiotherapy schedules in the Polish study indicated that the incidence of acute severe radiation induced toxicity (grades 3, 4, 5) was substantially higher following long course (18%) compared to SCPRT (3%).\textsuperscript{27} The incidence of severe late toxicity remained similar between groups: long course 7% versus SCPRT- 10%. Commonest severe late toxicity's with SCPRT were intestinal 5.1%, bladder 1.4%, sensory-motor disturbance 2.9% and femoral neck fracture 0.7%. No differences in overall survival, disease free survival or local recurrence were observed. Although the
German\textsuperscript{21} and Dutch\textsuperscript{6} studies did not directly compare preoperative radiotherapy schedules, the incidence of severe acute toxicity in these trials once again favoured SCPRT over CRT by a wide margin (3\% v 28\%). These data indicate that SCPRT is better tolerated than CRT in the short term with similar long-term effects. Use of SCPRT therefore seems preferable due to ease of administration and reduced acute toxicity with equivalent late toxicity.

**Efficacy of pelvic radiotherapy alone**

The cohort study of Habr-Gama et al\textsuperscript{28} comprised 265 patients with predominantly T3 rectal cancer treated initially by CRT. In 71 patients (27\%) a complete clinical response was observed. These patients were closely observed and not operated upon. With a mean follow up of 57 months (range 18-156 months), two patients developed local recurrence, one was successfully salvaged. A further three patients developed isolated distant metastases. The rate of pCR following radical surgery in those with an incomplete clinical response was 8\% (22 patients). To this point in time others have not independently replicated these findings. One problem has been a relatively poor correlation between clinical and pathological response in several studies.\textsuperscript{29,30} The work of Habr-Gama et al has, however, lead us to question whether radical surgery is the most effective curative treatment for all rectal cancer. A proportion of cases, particularly the early tumours, may be more efficiently treated using a conservative, organ preserving approach, following the paradigm of anal cancer.

**1.5. Efficacy of pelvic radiotherapy combined with local excision**

Combining pre-operative radiotherapy with TEM surgery is appealing as: (1) radiotherapy may effectively treat microscopic mesorectal nodal metastases, (2) tumour downsizing should facilitate local excision with clear margins, (3) tumour downstaging is measured objectively rather than relying upon clinical examination, and (4) histopathological non-responders are converted to radical surgery. There is currently very little evidence to guide the use of downstaging radiotherapy and local excision as curative treatment for early rectal tumours. Two small prospective studies have been conducted, the first comparing radical versus local excision following downstaging CRT,\textsuperscript{31} the second evaluated efficacy of long and short course neoadjuvant radiotherapy schedules prior to delayed local excision.\textsuperscript{29}

The study of Lezoche et al randomised 40 consecutive patients with T2N0 G1-2 rectal cancer to neoadjuvant CRT followed by either laparoscopic TME surgery or local excision using TEM after a 6-8 week interval.\textsuperscript{32} Patients were preoperatively staged using a combination of macro biopsy, ERUS and MRI. The pCR rate following CRT was 35\% (14 patients). A further 25\% (10 patients) were staged as ypT1. With a median follow up of 56 months (range 44-67 months), one from each group recurred (both ypT2). Salvage surgery was successful in the patient treated initially by organ preservation.
In the study of Bujko et al, 47 patients, with mainly T1 and T2 tumours (some early T3 allowed), received either neoadjuvant SCPRT or CRT prior to delayed local excision.\(^{29}\) Radiotherapy was usually followed by TEMS after a planned interval of 6 weeks (range 4-15 weeks) although other local excision techniques were allowed. Tumours were less than 4 cm in diameter, staged by digital rectal examination and MRI or ERUS/ pelvic CT. Three patients did not progress to local excision. The pCR rates were 35% (11/31) following SCPRT and 54% (7/13) after CRT. Histopathology indicated pCR or completely excised ypT1 tumour in 66% (29 patients). These patients were all then observed. The remainder (n=15) were candidates for conversion to radical surgery - of whom 7 were unfit or refused and one had a repeat local excision. APE was performed in 7 patients. Residual tumour was found within the bowel wall of 6 and one patient with ypT3 had mesorectal lymph node metastases. With median follow up of 14 months (range 0-41 months) local recurrence was detected in 3/44 operated patients (2x CRT, 1x SCPRT), all of whom underwent successful salvage surgery.

A meta-analysis of seven studies of CRT and local excision to treat 237 cT2-T3 rectal tumours, reported pCR rates of 22%\(^{33}\) with no local recurrences seen in this group. A further 19% of tumours were staged ypT1, 36% ypT2 and 14% ypT3 with local recurrence rates of 2%, 7% and 12% respectively.

**Safety of pelvic radiotherapy combined with local excision**

In the study of Bujko et al, grade I-II acute radiation toxicity was observed in 33% (11/31) patients treated with SCPRT and 64% (9/14) treated by CRT.\(^{29}\) Grade III toxicity occurred in a single patient treated by CRT. The most frequent complication was gastrointestinal toxicity. In the SCPRT group abdominal cramps, urgency and increased stool frequency occurred 3-7 days after completion of radiotherapy. In all but one patient these symptoms resolved within one week.

**Summary**

The literature supports use of downstaging radiotherapy and local excision as an alternative to radical surgery for curative treatment of early rectal cancers. Mortality is high following radical curative surgery for rectal cancer,\(^{7,8}\) and escalates as age and the incidence of comorbidity increase.\(^{8}\) Health related quality of life is persistently diminished following radical surgery.\(^{13-15}\) While recurrence rates following radical treatment for early rectal cancer are low, they are not zero. The literature supports estimates of 3-6%.\(^{3-5}\)

Local excision alone may be curative for the majority of early tumours, however, recurrence rates of 10-30% amongst higher risk lesions are unacceptable.\(^{16}\) There is currently no means to precisely identify cases that are likely to recur following local excision. Selective post-
operative radiotherapy for all tumours with less favourable histopathological characteristics does not produce satisfactory outcomes.\textsuperscript{16, 19}

It seems probable that a strategy of organ preservation using downstaging radiotherapy with an interval to excision biopsy using TEMS may produce substantial benefits in terms of reduced morbidity and mortality with long lasting improvements in quality of life. Due to low toxicity, SCPRT is an attractive treatment choice for these early tumours.\textsuperscript{27,29} Preliminary data suggest high rates of downstaging following SCPRT if surgery is delayed, in both early and advanced disease.\textsuperscript{26,29}

While we would not expect this strategy to be more effective than radical surgery, benefits in terms of reduced morbidity and improved long-term quality of life may outweigh a small increase in the risk of recurrence. Limited literature using pre-operative radiation with a long interval to local excision for T1 and T2 tumours would suggest that recurrence rates are low.\textsuperscript{29,31,33} Indeed, recurrence rates following organ preservation may be no higher than the combined incidence of perioperative mortality and recurrence in radically treated patients. Moreover, with optimized surveillance schedules we would hope to successfully salvage the majority of recurrences following local excision.

1.6. The need for TREC – Phase II trial of radical surgery versus organ preservation

With early stage disease becoming part of everyday practice, there is an opportunity to evaluate organ-preserving surgery. A feasibility study is, however, required before a definitive phase III randomised controlled trial (RCT) can be undertaken. The aim of the TREC pilot study is to determine the feasibility of randomising patients with MRI and an optional endorectal ultrasound (ERUS) staged early (T1-2N0M0) rectal cancer between radical TME surgery (current gold standard) and short course preoperative radiotherapy (SCPRT) with delayed local excision at 8-10 weeks.

Three main issues need to be addressed.

In the absence of good quality evidence, clinicians and patients often exhibit strong preferences for particular treatments. The pilot trial will explore patients’ and clinicians’ perceptions of trade-offs between oncological outcome, perioperative morbidity, post-operative function and quality of life. These will be used to estimate recruitment rates and inform stopping rules for a phase III trial.

Second, the degree of downstaging following pre-operative radiotherapy in an early rectal cancer population and the rate of conversion to radical surgery need to be defined to judge whether application of SCPRT is justified.
Third, a strategy of SCPRT plus delayed local excision must deliver tangible benefits over radical surgery in terms of reduced morbidity, improved functional outcome and quality of life in order to justify a larger trial. Tools to assess functional outcome and quality of life require evaluation with respect to their appropriateness for patients undergoing both radical and organ preserving treatment.

Data from the TREC pilot study will be used to provide standardised and detailed information for seeking consent to randomisation in the full phase III TREC trial.

2. OBJECTIVES

The aim of the TREC pilot study is to assess the feasibility and inform the design of a large, multi-centre randomised study comparing radical surgery versus radiotherapy plus local excision for early rectal cancer. Data will be obtained to allow accurate sample size estimation and to refine the primary outcome measures for the Phase III TREC trial.

2.1. Primary objective

- RECRUITMENT - Develop effective strategies for randomising patients between radical and local treatment for early rectal cancer.

2.2. Secondary objectives

- SAFETY - Compare morbidity/mortality and health related quality of life following radical surgery and SCPRT with delayed local excision.
- EFFICACY – Demonstrate that novel treatment with SCPRT and delayed local excision after an 8-10 week interval produces clear tumour downstaging.
- ACCEPTABILITY – Define risk-benefit boundaries within which patients and clinicians would accept randomisation.
3. TRIAL DESIGN
The TREC Phase II trial compares conventional TME surgery with short course preoperative radiotherapy (SCPRT) and delayed local excision with TEM (after an 8 – 10 week interval) for patients with early (T1 or T2 N0) rectal cancer defined according to MRI and an optional ERUS.

Outcome measures
The primary endpoint of the TREC pilot trial is:

- **RECRUITMENT** - measured at 12, 18 and 24 months

The secondary endpoints of the trial are:

- **SAFETY**
  - 30-day mortality
  - 6 month mortality
  - Surgical morbidity
  - Bowel, bladder and sexual function (measured by EORTC QLQ C29 & C30 and the Colorectal Functional Outcomes Questionnaire)

- **EFFICACY**
  - Histopathological assessment of tumour down-staging according to depth of tumour invasion and the incidence of other high-risk features
  - Conversion rates from organ conservation to radical surgery
  - Quality of life (measured by EORTC QLQ C29 & C30 and EuroQol EQ-5D at 3, 6, 12, 24, 36, 48 and 60 months post-operative)

4. PATIENT ENTRY

4.1. Screening of potential participants
It is envisaged that patients will be recruited to TREC from the colorectal surgical clinic following referral in through one of three pathways:

1. UK Bowel Cancer Screening Programme
2. GP referral
3. Tertiary referral

Recruitment will be a two-stage process. At their first colorectal clinic appointment, patients with early rectal cancer will be seen by a colorectal surgeon to confirm their diagnosis. At this first appointment, all possible treatment options will be explained and if, in the surgeon’s opinion and based on the preliminary investigations, the patient may meet the eligibility criteria, the TREC trial will be introduced as one possibility. The patient should be given a
patient information leaflet (Appendix A) from the TREC trial pack so that patients can find out more about the study before deciding whether or not to participate. The patient will then have further radiological, endoscopic and histopathological investigations as required and return for a second colorectal clinic appointment 1 – 4 weeks later to discuss possible entry into TREC.

4.2. Eligibility criteria

Inclusion criteria
- Biopsy proven adenocarcinoma
- MRI defined stage I rectal cancer (< T3 N0)
- Endorectal ultrasound defined rectal cancer < uT3 (optional)
- Patients who have undergone submucosal excision for a presumed villous adenoma that on histopathological examination contains discrete invasion ≤ 30mm in maximum diameter
- Aged 18 or over

Exclusion criteria
- T3+ or nodal involvement on radiological staging
- Contraindications to radiotherapy
- Previous pelvic radiotherapy
- Metastatic disease
- Patients who are pregnant or lactating
- Unable or unwilling to provide written informed consent

5. CONSENT AND RANDOMISATION

5.1. Informed consent
If the patient is considered eligible for TREC, the surgeon and/or research nurse will discuss the trial in detail with the patient at the second surgical clinic appointment. Before doing so, the patient should be asked for consent to tape-record the discussion (Appendix B). A checklist is provided in the TREC study folder to facilitate this information appointment. After a full explanation has been given of the treatment options, and the manner of treatment allocation, all suitable patients should be invited to take part in the randomised component of the trial but it is important not to put undue pressure on the patient. If the patient and/or the surgeon do not consider randomisation appropriate, then the patient will be asked for consent to enter the TREC registry only, ie to complete baseline and follow-up Quality of Life questionnaires and to allow collection of treatment outcome data. Consent for the randomisation or registry may be
by either the surgeon, oncologist or the nurse. For patients who are entered into the registry, rather than randomised, the reasons for treatment preference should be recorded.

The conduct of the trial will be in accordance with the Research & Governance Framework for Health and Social Care and ICH GCP. Patients should have at least 24 hours to consider whether to take part in the TREC randomisation. The patient's written consent to participate in TREC must be obtained before randomisation or registration. The original signed Consent forms (Appendix C) should be kept in the TREC study file, one copy for the patient, one kept on the patient's notes and one sent to the TREC Study Office.

5.2. Telephone & out of hours randomisation
Patients are entered in the trial by telephone call to the randomisation service (telephone number 0800 9530274, toll-free in the UK, or +44 (0) 121 415 9137 from elsewhere) or by internet at: https://www.trials.bham.ac.uk/TREC

Telephone randomisation is available Monday-Friday 0900-1700 UK time. Randomisation out of these hours is obtained by logging on to the TREC website. Each centre and each randomiser will be provided with a unique log-in and password to do this. Randomisation notepads (Appendix E) are provided in the TREC study folder and should be used to collate the necessary information prior to randomisation. After all the necessary details have been provided, the treatment allocation will be specified at the end of the telephone call. The patient's GP should be notified that they are in TREC, and a specimen "Letter to GP" is provided for this purpose (Appendix D).

5.3. The non-randomised registry
Entry on to the registry
Ideally all eligible patients should be randomised. If, however, there is considered to be a definite indication for either radical TME surgery or organ preservation for a particular patient, they should be entered on to the TREC registry prospectively. Patients entering the registry should be counselled in the same way as those for the RCT, provided with the patient information leaflet and consented in the same manner. Entry onto the registry will be via telephone or internet registration, as for randomisation (see above), with all information on the randomisation notepad required. The follow up of registry participants will also be the same as for randomised patients.

The importance of the registry
The registry arm of the study is part of a comprehensive cohort design with data collection on all potentially eligible patients including those whose choice of surgery is not randomised. Gaining a better understanding of the factors influencing clinicians’ uncertainty about
appropriate surgery and patient’s preferences is an important part of the TREC pilot study. The registry will also allow evaluation of health related quality of life instruments in a larger group of patients and will provide important additional data regarding the relative safety of each treatment.

6. TREATMENT

6.1. Surgical resection

Experimental Arm – Local excision
Accomplished either by Transanal Endoscopic Microsurgery (TEM) or Transanal Endoscopic Operation (TEO) using standard techniques. Very low tumours may be resected using a composite of TEM/TEO and Parks peranal excision. TEM is a modified technique of local excision for rectal tumours. This method greatly improves accessibility, visualisation and precision of resection of early rectal tumours. The surgeon works via a 40mm proctoscope using magnified binocular vision. The rectum is insufflated with carbon dioxide and laparoscopic style tools are introduced through airtight ports. The rectal lesion is removed by sharp dissection under direct vision with a 1cm margin of normal tissue. Both tumour and underlying muscular wall of the rectum are removed en-bloc.

Control arm – Radical excision
Performing either abdominoperineal excision or anterior resection using either total mesorectal or, in appropriate cases, partial mesorectal excision.

6.2. Short Course Preoperative Radiotherapy - SCPRT (Experimental arm)
Full details of radiotherapy are provided in Appendix F. In brief, a dose of 5 Gy per fraction will be delivered, to a total dose of 25 Gy in 5 fractions over a period of 5 days. The use of 3-D conformal radiotherapy is recommended with simple coplanar or combination of coplanar and non-coplanar conformal deliverable fields. The use of at least three to four beams is recommended to decrease the volume of small bowel in the irradiated volume. All fields must be treated during one treatment session. Radiation therapy must be delivered by photon radiation generated by a linear accelerator with effective photon energies ≥ 6 MV. Equipment of 10 MV or higher is strongly recommended. It is essential to encompass the gross tumour, potential areas of microscopic spread as well as pelvic lymph nodes at risk of involvement within the clinical target volume (CTV). As the mesorectal lymph nodes are not removed during the surgical technique of TEMS, these must be treated by radiotherapy. Specific planning diagrams will be produced to define the approach according to tumour position.
6.3. Histological evaluation of resection specimen

Histopathological assessment of high-risk features in TEMS specimens will be key to the TREC study. Patients who exhibit high-risk features following SCPRT will be strongly considered for conversion to radical surgery. The oncological efficacy of SCPRT and delayed local excision will be estimated using the relative incidence of high-risk histopathological features in irradiated versus non-irradiated specimens. Further more detailed explanation can be found in Appendix K.

Assessment of high-risk histopathological features

The high-risk features that we have selected as indicators for consideration of conversion to radical surgery are identified in the figure. For further details regarding standardised assessment and measurement please refer to Appendix K.

Conversion from organ preservation to radical surgery

While the presence of one or more high-risk features does not compel conversion to radical surgery, the surgical team will discuss the implications of the high risk features and the expected benefits of conversion to radical surgery with patients who demonstrate these features in the resected specimen. Those patients who decide to undergo conversion will have radical surgery performed in a timely fashion, generally within 8 weeks of the initial TEMS/TEO procedure.

6.4. Blood and tumour sample collection

Blood samples

A 20 ml EDTA blood sample will be collected prior to treatment if the patient has consented for this at trial entry. This blood sample will be used in translational research. The blood sample should be labelled with the patient’s initials, TREC trial number and date of birth but not with their name. The tube(s) should be sealed and sent in the prepaid, safe box provided by the TREC study office and posted to:
TREC Trial laboratory, Leeds Institute of Molecular Medicine, Section of Pathology & Tumour Biology, Wellcome Trust Brenner Building, St James’s University Hospital, Leeds, LS9 7TF.

**H&E slides**

Either the original glass slides or a duplicate set of H&E slides of the diagnostic pre-operative biopsy and any resected tumour should also be prepared and sent to the TREC trials office along with a copy of the pathology report labelled with the patient’s initials and TREC trial number but not their name. These will be logged and anonymised prior to sending to the TREC lab in Leeds, where they will then be scanned prior to returning to the originating hospital in the same state in which they were taken. Place the slides in a suitable container with adequate packaging to prevent breakage and place in a jiffy bag together with the pathology report and send to:

TREC Study Office, Birmingham Clinical Trials Unit, Robert Aitken Institute, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT.

**Paraffin-embedded tissue blocks**

Provided the patient has consented to their tissue removed at surgery being used for research, paraffin-embedded blocks will be collected for all patients undergoing either TEM/TEO or TME. These will be used to study candidate biomarkers for prediction of treatment outcome. A FFPE tumour block and a normal mucosal block plus the associated pathology report should be labelled with the patient’s initials and TREC trial number but not their name and sent to the TREC study office. Place the samples in a sealed envelope and place in a jiffy bag together with the pathology report and send to:

TREC Study Office, Birmingham Clinical Trials Unit, Robert Aitken Institute, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT.

The blocks, H&E slides and pathology report will then be logged, anonymised and forwarded to the TREC lab in Leeds.

**Fresh-frozen tissue**

Provided the patient has consented to their tissue being used for research, fresh tissue will be collected and immediately frozen in liquid nitrogen at the time of pre-treatment endoscopic assessment and at TEM/TEO or TME surgery. These will be used to study candidate biomarkers for prediction of treatment outcome.

### 6.5. Compatibility with other studies

TREC is currently the only study in the NCRI trials portfolio to evaluate novel treatment strategies in early rectal cancer.
6.6. Assessment schedule

Trial data will be recorded by hospital research staff on the Case Report Forms (CRFs) and submitted to the TREC Study office at BCTU.

Radiotherapy will be administered as per the RT QA protocol (Appendix F) and radiotherapy delivery and toxicities up to 3 weeks after the completion of radiotherapy will be recorded on the Radiotherapy Delivery Form and Radiotherapy Toxicity Form (Appendices G and H). Surgical morbidity will be recorded intra-operatively on the Intraoperative Form (Appendix I) and post-operative complications should be recorded 30-days post-op on the Surgical Review Form (Appendix J). Quality of Life forms (Appendices M and N) and the colorectal functional outcome (COREFO) questionnaire (Appendix O) should be completed prior to start of treatment and then at 3, 6, 12, 24, 36, 48 and 60 months post-operatively. This information will be supplemented, where possible, by the use of national mortality records to ensure long-term follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Prior to patient entry</th>
<th>After radiotherapy</th>
<th>Prior to 1st treatment</th>
<th>30-days post-op</th>
<th>3 months post-op</th>
<th>6 months post-op</th>
<th>12 months post-op</th>
<th>24 months post-op</th>
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<tr>
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<td>Annual follow-up</td>
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<tr>
<td>Adverse Events</td>
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<td>Monitor throughout the course of the study</td>
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</table>

a. Prior to first treatment means prior to radiotherapy if randomised to SCPRT plus local excision or prior to surgery if randomised to TME.
b. Endorectal ultrasound and pelvic MRI should be performed for all patients prior to randomisation and this should be within 3 months of randomisation.
c. Radiotherapy details to be recorded on the Radiotherapy Delivery Form; Radiotherapy Toxicity Form will record radiotherapy toxicities 2-3 weeks after completion.
d. Surgical morbidity will be recorded intra-operatively on the Intraoperative Form and at 30 days post-op on the Surgical Review Form and at 3, 6 and 12 months.
e. Blood samples taken as routine haematology and tumour tissue from the resection specimen will be analysed for biomarkers. Resected specimen will be evaluated in line with standardised method (Appendix K).
f. Both QoL and annual follow-up will continue until 60 months post-op.

6.7. Clinical follow-up

Follow-up after surgery will include regular clinical follow-up as per usual practice. The recommended follow-up is detailed in the table below. The information routinely recorded in normal clinical notes should be sufficient for completion of the annual follow-up forms (Appendix Q).
• CEA assessed annually
• Baseline post-operative pelvic MRI 3 months following TEMS
• Baseline post-operative sigmoidoscopy 3 months following TEMS
• Post-operative pelvic MRI annually for the first 3 years following TEMS (further pelvic MRI as clinically indicated)
• Post-operative sigmoidoscopy at 6, 9, 12, 18 and 24 months
• Colonoscopy at 36 months (all patients)
• The information routinely recorded in normal clinical notes should be sufficient for completion of the annual follow-up forms (Appendix Q).

<table>
<thead>
<tr>
<th></th>
<th>Prior to patient entry</th>
<th>After RT</th>
<th>3 months post-op</th>
<th>6 months post-op</th>
<th>9 months post-op</th>
<th>12 months post-op</th>
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</table>

a. Performance status (WHO criteria) will also be assessed
b. ERUS (optional) and pelvic MRI will be performed for all patients prior to trial entry and this should be within 3 month of trial entry.
c. MRI and sigmoidoscopy will be performed at 3 and 6-months post-operatively for TEMS patients
d. Pelvic MRI will be performed annually for first 3 years for TEMS patients

6.8. The end of the study

The end of the TREC study for regulatory purposes is defined as the date of the last visit of the last patient undergoing the protocol based therapy. Long-term follow-up, to at least 5 years after randomisation of the last patient, constitutes the non-interventional phase of the trial.

Documents will be retained for a period of 13 years following randomisation. This will enable late disease recurrence to be captured at 10 years in the novel treatment arm.

7. SAFETY MONITORING PROCEDURES

Within the TREC trial, an SAE is defined as an untoward occurrence that:

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

For the purposes of this study, adverse events include, **but are not limited to:**
• Post-operative haemorrhage requiring transfusion or return to theatre
• Pelvic abscess or fistula
• Clinically detected anastomotic leakage

**Reporting AEs**
From the first administration of trial treatment until 3 weeks after the last trial treatment, all toxicities related to the underlying rectal cancer or its treatment, whether observed directly or reported by the patient, will be collected and recorded on the Radiotherapy Toxicity Form (Appendix H).

**Reporting SAEs**
Serious adverse events believed to be due to surgery or to SCPRT should be reported on a Serious Adverse Event Form (Appendix P) and faxed to the TREC study office (+00 44 121 415 8871). SAEs still present at the end of the study must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient finishes the study treatment and, when appropriate, until the end of the planned period of follow-up. The BCTU will report all SAEs to the DMEC approximately 3-monthly, to the main REC annually, and to the Trial Steering Committee 6-monthly. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform the main REC as this will be done by the BCTU.

**8. SIZE, STATISTICS & DATA MONITORING PROCEDURES**
A total of 46 patients need to be randomised to demonstrate that SCPRT reduces the incidence of ‘high risk’ features (see section 6.3) from 75% to 35% (α=0.05, power=0.8, one-tailed). This number would also provide 90% power at p<0.01 to detect a large (1 sd) effect size difference in quality of life measures between TME and SCRT plus conservative surgery. Effects of this magnitude combined with low conversion rates from local to radical TME surgery would provide strong justification for further investigation in a Phase III trial. Since this study is designed as a pilot trial, we have not performed any estimation of the sample size required for the full trial. The purpose of the pilot study is to identify if recruitment to the full trial would be feasible and also to refine outcome measures. To inform our choice of primary endpoint for the full trial, we will measure a variety of outcomes in the pilot study including
pathological downstaging of tumours and quality of life using the QLQ-C30 questionnaire. The frequency and magnitude of downstaging/downsizing in early rectal cancer, and whether the proportion of incomplete resections is reduced by SCPRT, is unknown. The data obtained from the pilot study will inform power analyses for the phase III trial.
9. ORGANISATION
To ensure the smooth running of TREC and to minimise the overall procedural workload, it is proposed that each centre should designate individuals who would be chiefly responsible for local coordination of clinical, pathological and administrative aspects. The TREC Trial Office, working together with NCRN networks, will provide as much assistance as they can to local co-ordinators and investigators in obtaining Trust approval in each centre, by providing lists of local surgeons and oncologists who have expressed interest, and helping resolve any local problems that may be encountered.

9.1. Principal investigator at each site
Each TREC site should nominate one person to act as the local Principal Investigator. The responsibilities of the local Principal Investigator will be to ensure that conduct of the research at their centre follows the agreed protocol and that all medical and nursing staff involved in the care of rectal cancer patients are well informed about the study and trained in trial procedures, including obtaining informed consent. The local PI is also responsible for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse events or suspected misconduct through the appropriate systems. The local Principal Investigator should liaise with the TREC Trial Coordinator on logistic and administrative matters connected with the trial.

9.2. Central coordination: supply of trial materials, 24-hour randomisation, data collection and analysis
The TREC Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing collaborating centres with the TREC folders containing trial materials. The TREC Study Office will assist the local Principal Investigators in obtaining local Trust approval. Patient entry in a centre can start as soon as management approval is given. Additional supplies of printed materials can be obtained on request. The TREC Study Office also provides the 24-hour randomisation service and is responsible for collection of data (including reports of serious adverse events thought to be due to trial treatment) and for data analyses.

9.3. Clinical queries
During office hours, the clinical coordinators (see inside front cover for contact details) provide an on-call service for any clinical queries about the trial.
9.4. Finance
TREC is funded by Cancer Research UK and organised by the Department of Health funded University of Birmingham Clinical Trials Unit. The general structure of the study was designed by the Surgical Trials Subcommittee of the UK National Cancer Research Institute’s Colorectal Cancer Clinical Studies Group and the BCTU.

9.5. Cost implications
The TREC trial can offer no financial support to the collaborating hospitals for treatments. However, TREC should not involve any extra research costs for participating hospitals. The current standard of care is selective pre-operative radiotherapy followed by total mesorectal excision. No additional follow-up visits or investigations are needed other than those that would normally be required for standard patient care.

9.6. Indemnity
TREC was developed by the NCRI colorectal cancer Clinical Studies Group and is funded by Cancer Research UK; the University of Birmingham is the trial ‘sponsor’. As it is not an industry-sponsored trial, ABPI guidelines on indemnity do not apply and there are no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity liability arrangements for clinician initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.

9.7. Publication
A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of TREC depends on the collaboration of many surgeons, radiotherapists and nurses. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study.
10. REFERENCES


