



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.

Protocol v1.0 15th September 2010

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

Trials Management

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

Data Monitoring and Ethics Committee

Pathology

Professor Phillip Quirke
St James's University Hospital, Leeds
Philip.quirke@leedsth.nhs.uk

Dr Bryan Warren
John Radcliffe Hospital, Oxford
Bryan.warren@orh.nhs.uk

Radiotherapy

Dr Ian Geh
Heartlands Hospital, Birmingham
ian.geh@hoe.nhs.uk

Dr David Sebag-Montefiore
St James's University Hospital, Leeds
David.sebagmontefiore@leedsth.nhs.uk

Dr Arthur Sun-Myint
Clatterbridge Hospital, Wirral
Arthur@sunmyint.co.uk

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

Statistics

Professor Richard Gray
Birmingham Clinical Trials Unit
r.gray@bham.ac.uk

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

Trial Steering Committee

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	hilkennh@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

MREC number: ; **ISRCTN number:** 14422743; **Protocol version:** 1.0 15/09/2010

CONTENTS

1. BACKGROUND	1
1.1. Increasing incidence of early rectal cancer poses new surgical dilemma	1
1.2. Benefits and risks of radical TME surgery	1
1.3. Local excision alone for early rectal cancer	1
1.4. Pelvic radiotherapy	2
1.5. Efficacy of pelvic radiotherapy combined with local excision	3
1.6. The need for TREC – Phase II trial of radical surgery versus organ preservation	5
2. OBJECTIVES	6
2.1. Primary objective	6
2.2. Secondary objectives	6
3. TRIAL DESIGN	7
4. PATIENT ENTRY	7
4.1. Screening of potential participants	7
4.2. Eligibility criteria	8
5. CONSENT AND RANDOMISATION	8
5.1. Informed consent	8
5.2. Telephone & out of hours randomisation	9
5.3. The non-randomised registry	9
6. TREATMENT	
6.1. Surgical resection	10
6.2. Short Course Preoperative Radiotherapy - SCPRT (Experimental arm)	10
6.3. Histological evaluation of resection specimen	11
6.4. Blood and tumour sample collection	11
6.5. Compatibility with other studies	12
6.6. Assessment schedule	12
6.7. Clinical follow-up	13
6.8. The end of the study	14
7. SAFETY MONITORING PROCEDURES	14
8. SIZE, STATISTICS & DATA MONITORING PROCEDURES	15
9. ORGANISATION	16
9.1. Principal investigator at each site	16
9.2. Central coordination: supply of trial materials, 24-hour randomisation, data collection and analysis	16
9.3. Clinical queries	16
9.4. Finance	17
9.5. Cost implications	17
9.6. Indemnity	17
9.7. Publication	17
10. REFERENCES	18

APPENDICES

A -	Patient Information Sheet	20
B -	Consent form	26
C -	GP Letter	27
D -	Randomisation notepad	28
E -	Administration of Short Course Preoperative Radiotherapy (SCPRT)	29
F -	Radiotherapy Delivery Form	33
G -	Radiotherapy Toxicity Form	34
H -	Intraoperative Form	36
I -	Surgical Review Form	37
J -	Pathology Protocol	38
K -	Proforma for local excision specimens	44
L -	EQ-5D Quality of Life questionnaire	45
M -	EORTC QLQC29 & QLQCR30 Quality of Life questionnaire	48
N -	Colorectal Functional Outcome (COREFO) questionnaire	52
O -	Serious Adverse Event Form	64
P -	Annual Follow-up Form	66

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).^{1,2} While radical total mesorectal excision (TME) is a highly effective treatment for symptomatic rectal cancer, as only 3-6% of patients experience local relapse,³⁻⁵ mortality from the procedure is significant at 3-4%^{6,7} 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 1990.⁸ These findings are consistent with those of the Association of Coloproctology of GB&I audit.⁷ 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.⁹ Pelvic dissection may inadvertently cause autonomic nerve damage leading to urinary incontinence or retention (25%-34%) and sexual dysfunction.^{10,11} More than half of all patients experience some form of faecal incontinence following TME surgery and 30-40% suffer daily symptoms of urgency, incomplete emptying and stool frequency.^{11,12} Three prospective cohort studies have examined health related quality of life scores following rectal cancer surgery.¹³⁻¹⁵ 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).^{16,17} 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^{3,4,18} and the rate of local failure following TEMS¹⁶ 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.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.¹⁶ Conversion of all intermediate risk patients to radical surgery would provide no additional benefit for the majority, although taking no further action would result in unacceptable levels of recurrence. Selective post-operative radiotherapy for 'high-risk' cases has failed to deliver satisfactory improvements in disease control.^{16,19} Pre-operative radiotherapy is more effective than post-operative radiotherapy^{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.^{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.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.²⁴ However SCPRT may effectively downstage locally advanced tumours if surgery is delayed.^{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%).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

German²¹ and Dutch⁶ 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 al²⁸ 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.^{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,³¹ the second evaluated efficacy of long and short course neoadjuvant radiotherapy schedules prior to delayed local excision.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.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.^{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.^{27,29} Preliminary data suggest high rates of downstaging following SCPRT if surgery is delayed, in both early and advanced disease.^{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.^{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 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

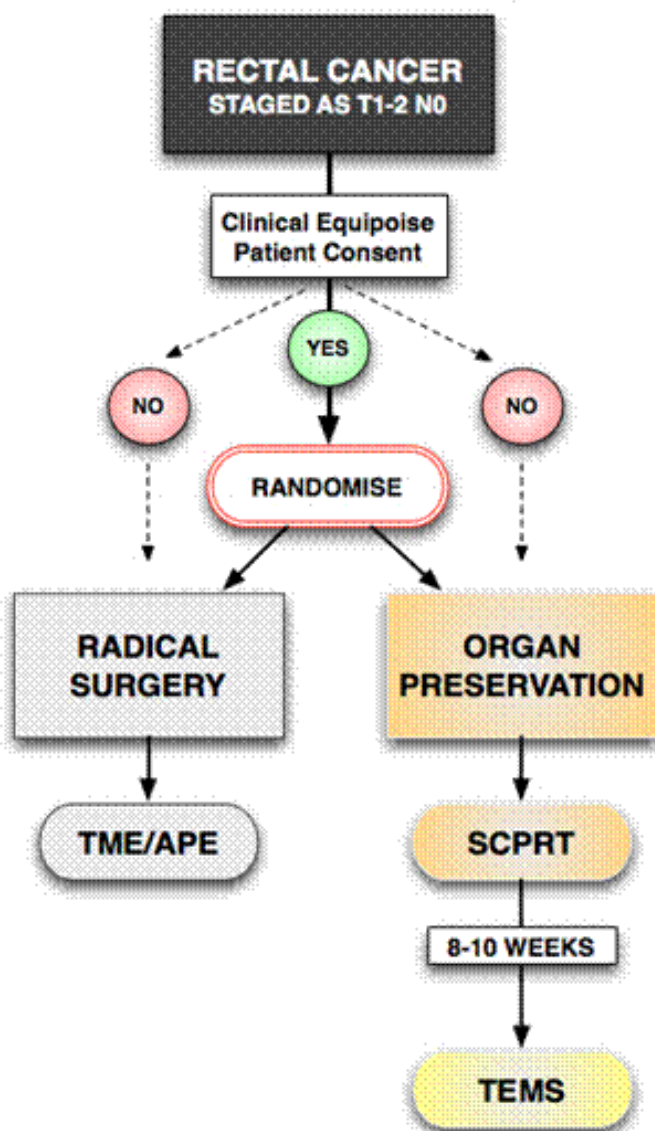
The aim of the **TREC** pilot study is to assess the feasibility and inform the design of a large, multi-centre randomised study comparing radical surgery versus radiotherapy plus local excision for early rectal cancer. Data will be obtained to allow accurate sample size estimation and to refine the 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 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
- Patients who have undergone submucosal excision for a presumed villous adenoma that on histopathological examination contains discrete invasion \leq 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. 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 B) 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 D) 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 C).

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.³⁵ Very low tumours may be resected using a composite of TEM/TEO and Parks perianal 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 E. 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

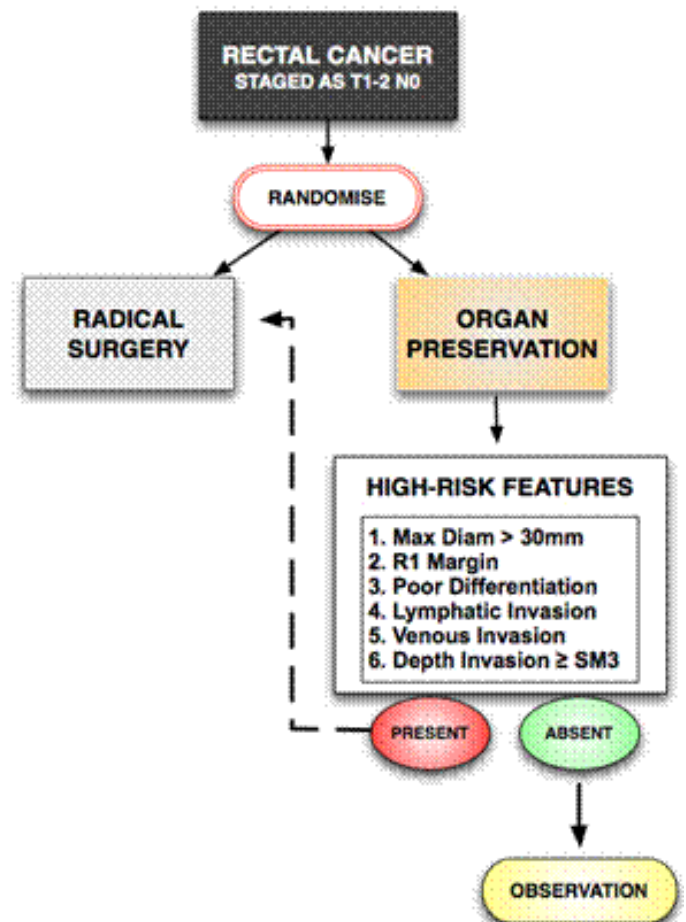
Histopathological assessment of high-risk features in TEMS specimens will be key to the TREC study. Patients who exhibit high-risk features following SCPRT will be strongly considered for conversion to radical surgery. The oncological efficacy of SCPRT and delayed local excision will be estimated using 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

A duplicate set of H&E slides of the diagnostic biopsy and any resected tumour should also be prepared and sent to the **TREC** trials office. 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.

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 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 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 Appendix F and radiotherapy delivery and toxicities up to 3 weeks after the completion of radiotherapy will be recorded (Appendix F and G). Surgical morbidity will be recorded intra-operatively (Appendix H) and post-operative

complications should be recorded 30-days post-op on the surgical review form (Appendix I). Quality of Life forms (Appendix L, and M) 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.

	Prior to patient entry	After radiotherapy	Prior to 1 st treatment ^a	30-days post-op	3 months post-op	6 months post-op	12 months post-op	24 months post-op
Informed Consent/ Entry onto TREC registry	X							
Radiological imaging ^b	X							
Radiotherapy delivery & toxicity		X ^c						
Surgical morbidity				X ^d	X	X	X	
Histopathology ^e	X			X				
Quality of Life ^f			X		X	X	X	X
Annual follow-up ^f							X	X
Adverse Events ^g	Monitor throughout the course of the study							

- Prior to first treatment means prior to radiotherapy if randomised to SCPRT plus local excision or prior to surgery if randomised to TME.
- Endorectal ultrasound and pelvic MRI should be performed for all patients prior to randomisation and should be within 3 months.
- Radiotherapy details to be recorded on Appendix F; Appendix G to record radiotherapy toxicities 2-3 weeks after completion.
- Intra-operatively (Appendix H) and at 30 days post-op (Appendix I) and at 3, 6 and 12 months.
- 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)
- 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 P).

- 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 27 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 P).

	Prior to patient entry	After RT	3 months post-op	6 months post-op	9 months post-op	12 months post-op	18 months post-op	24 months post-op	36 months post-op
Medical history	X								
Clinical evaluations including physical examination	X	X ^a	X	X		X		X	X
Endorectal ultrasound	X ^b								
MRI	X ^b		X ^c	X		X ^d		X ^d	X ^d
Colonoscopy									X
Sigmoidoscopy			X ^c	X	X	X	X	X	
CEA						X		X	X
CT scan						X		X	

- a. Performance status (WHO criteria) will also be assessed
- b. ERUS and pelvic MRI will be performed 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 G).

Reporting SAEs

Serious adverse events believed to be due to surgery or to SCPRT should be reported on a Serious Adverse Event form (Appendix O) 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% ($\alpha=0.05$, 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 LREC and 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

1. UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002;**359**(9314): 1291-1300.
2. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. *BMJ* 2004;**329**(7458): 133.
3. Bentrem DJ, Okabe S, Wong WD, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? *Ann Surg* 2005;**242**(4): 472-477; discussion 477-479.
4. Endreseth BH, Myrvold HE, Romundstad P, et al. Transanal excision vs. major surgery for T1 rectal cancer. *Dis Colon Rectum* 2005;**48**(7): 1380-1388.
5. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007;**246**(5): 693-701.
6. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al, Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**(9): 638-646.
7. Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: prospective national study. *BMJ* 2003;**327**(7425): 1196-1201.
8. Rutten HJ, den Dulk M, Lemmens VE, et al. Controversies of total mesorectal excision for rectal cancer in elderly patients. *Lancet Oncol* 2008;**9**(5): 494-501.
9. Marijnen CAM, Kapiteijn E, van de Velde CJH, et al, Cooperative Investigators of the Dutch Colorectal Cancer Group. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002;**20**(3): 817-825.
10. Hendren SK, O'Connor BI, Liu M, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Ann Surg* 2005;**242**(2):212-223.
11. Wallner C, Lange MM, Bonsing BA, et al. Causes of Fecal and Urinary Incontinence After Total Mesorectal Excision for Rectal Cancer Based on Cadaveric Surgery: A Study From the Cooperative Clinical Investigators of the Dutch Total Mesorectal Excision Trial. *J Clin Oncol* 2008;**26**(27): 4466-4472.
12. Temple LK, Bacik J, Savatta SG, et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. *Dis Colon Rectum* 2005;**48**(7): 1353-1365.
13. Engel J, Kerr J, Schlesinger-Raab A, et al. Quality of life in rectal cancer patients: a four-year prospective study. *Ann Surg* 2003;**238**(2): 203-213.
14. Grumann MM, Noack EM, Hoffmann IA, Schlag PM. Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer. *Ann Surg* 2001;**233**(2): 149-156.
15. Wilson TR, Alexander DJ. Clinical and non-clinical factors influencing postoperative health-related quality of life in patients with colorectal cancer. *Br J Surg* 2008;**95**(11): 1408-1415.
16. Bach SP, Hill J, Monson JR, et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. *Br J Surg* 2009;**96**(3): 280-290.
17. Cataldo PA, O'Brien S, Osler T. Transanal endoscopic microsurgery: a prospective evaluation of functional results. *Dis Colon Rectum* 2005;**48**(7): 1366-1371.
18. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002;**45**(2): 200-206.
19. Greenberg JA, Shibata D, Herndon JE, et al. Local excision of distal rectal cancer: an update of cancer and leukemia group B 8984. *Dis Colon Rectum* 2008;**51**(8): 1185-1191; discussion 1191-1184.

20. Sauer R, Becker H, Hohenberger W, et al, German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**(17): 1731-1740.
21. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009;**373**(9666): 811-820.
22. Dahlberg M, Glimelius B, Pahlman L. Improved survival and reduction in local failure rates after preoperative radiotherapy: evidence for the generalizability of the results of Swedish Rectal Cancer Trial. *Ann Surg* 1999;**229**(4): 493-497.
23. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol* 1999;**17**(8): 2396.
24. Marijnen CA, Nagtegaal ID, Klein Kranenbarg E, et al, Pathology Review Committee and the Cooperative Clinical Investigators. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001;**19**(7): 1976-1984.
25. Graf W, Dahlberg M, Osman MM, et al. Short-term preoperative radiotherapy results in down-staging of rectal cancer: a study of 1316 patients. *Radiother Oncol* 1997;**43**(2): 133-137.
26. Radu C, Berglund K, Pahlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer - a retrospective study. *Radiother Oncol* 2008;**87**(3): 343-349.
27. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;**93**(10): 1215-1223.
28. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004;**240**(4): 711-717; discussion 717-718.
29. Bujko K, Richter P, Kolodziejczyk M, et al. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders. *Radiother Oncol* 2009;**92**(2):195-201.
30. Guillem JG, Chessin DB, Shia J, et al. Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point. *J Clin Oncol* 2005;**23**(15): 3475-3479.
31. Lezoche E, Guerrieri M, Paganini AM, et al. Long-term results in patients with T2-3 N0 distal rectal cancer undergoing radiotherapy before transanal endoscopic microsurgery. *Br J Surg* 2005;**92**(12): 1546-1552.
32. Lezoche E, Guerrieri M, Paganini AM, et al. Transanal endoscopic versus total mesorectal laparoscopic resections of T2-N0 low rectal cancers after neoadjuvant treatment: a prospective randomized trial with a 3-years minimum follow-up period. *Surg Endosc* 2005;**19**(6): 751-756.
33. Borschitz T, Wachtlin D, Möhler M, et al. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. *Ann Surg Oncol* 2008;**15**(3): 712-720.
34. Ota DM, Nelson H. Local excision of rectal cancer revisited: ACOSOG protocol Z6041. *Ann Surg Oncol* 2007;**14**(2): 271.
35. Buess G, Kipfmüller K, Hack D, et al. Technique of transanal endoscopic microsurgery. *Surg Endosc*. 1988;**2**(2):71-5.

APPENDIX A - PATIENT INFORMATION SHEET

Delete this line, then print on Trust headed paper

TREC – Transanal Endoscopic Microsurgery (TEM) and Radiotherapy in Early Rectal Cancer - Patient Information Sheet, Version 2.0 2nd December 2010

Information on a research study called TREC

- Tests have shown that you have a small cancer in your rectum. Fortunately, this cancer is at an early stage, which means that there is a very good chance it can be cured by surgery.
- Your medical team is making further investigations and, after the results of these are known, they will discuss with you which of two possible operations would be best for you.
- The standard operation, called radical surgery, is to remove the entire rectum. We know that radical surgery cures 95% of cancers but it can result in serious side-effects or, rarely, death.
- A new approach for small cancers like yours is to treat the rectum first with radiotherapy for one week and then to wait 8-10 weeks to allow time for the cancer to shrink. A smaller operation is then performed through the anus to remove the area affected by cancer. The rest of the rectum and the anus are left alone. If radiotherapy has worked well and the cancer is very small or has completely disappeared then no further treatment is given. If your cancer does not respond well to radiotherapy, though, then radical surgery may be needed.
- We hope that patients treated with this new approach will experience fewer side effects and have better quality of life compared to those treated by standard radical surgery. But, we can't be sure about this yet, and the disadvantage of the smaller operation is that there may be a greater risk of the cancer coming back in the future, which may then be harder to treat.
- A third option that we will discuss with you if, after the further investigations, your doctors think that you would be suitable for either of these two treatments is to take part in a research study called **TREC**, which aims to find out whether the new treatment is better than standard radical surgery for patients with small rectal cancers.
- People who take part in **TREC** are assigned to one of the two treatments at random (like a lottery) with one group getting radical surgery and the other the new type of treatment. This is called a clinical trial and it is the standard and most reliable way to compare treatments.
- Taking part in research studies like **TREC** is, of course, optional and if you were invited to take part but decided not to, your medical team would not think badly of you and it would not affect the quality of your care.
- We will arrange another appointment for you to discuss treatment options with your medical team when, between you, you can choose the one that seems best for you. Whether or not you take part in the **TREC** clinical trial, we would still like to collect data on how the treatment affects you and use this information to help improve treatment of future patients.

Delete this line, then print on Trust headed paper

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

Patient Information Sheet

Version 2.0 2nd December 2010

Invitation to take part in a research study called TREC

You are being invited to take part in a research study. Before you decide, it is important to understand why the research is being done and what it will involve. This information sheet provides you with a detailed description of the study so that you can think about whether you want to take part, and discuss it with others if you wish.

Part 1: Purpose of the study and what will happen to you if you take part

What is the purpose of the TREC study?

The aim of the **TREC** study is to find the best way of treating a small rectal cancer. We will compare two different treatments. Standard treatment involves a big operation (called radical surgery) to remove the whole rectum. The new approach uses radiotherapy to first shrink the cancer before a small 'keyhole' operation is done to remove it through the anus. With this new treatment only the area directly affected by cancer is removed. The rest of the rectum and the anus are left alone. While we believe that the new approach is likely to have fewer side effects than standard treatment, not many patients have been treated this way, so we do not know if it will be as effective at curing cancer.

TREC is planned in two stages:

The first stage, which you are being invited to take part in, will tell us how effective radiotherapy is at shrinking tumours, what proportion of small cancers can then be removed by a small operation and how the new treatment affects people's bowel function and quality of life compared to standard treatment. We also want to ask people with early rectal cancer what is most important to them in deciding the choice of treatment and whether they are willing to have their treatment choice made as part of the research study to find out reliably which treatment is best.

As part of this first stage of **TREC** we are also trying to improve how we communicate with patients to make sure that they understand the discussions about their cancer, all the possible treatment options, the advantages and disadvantages of each, and why studies like **TREC** are needed to find out which treatments are best. For this part, some patients will be asked for their consent to tape record or video tape their second appointment with their doctor and then to be asked some questions afterwards about what they understood from the meeting. Patients do not have to be recorded if they prefer not to be and patients being recorded will be asked to sign a consent form to confirm their agreement to this.

If the first part of the **TREC** study is completed successfully, the second stage of the study will directly compare the risks and benefits of each of the treatments used in **TREC** so we can be certain of which is best. This part of the study will require many more patients and will be informed by the results of the first study.

Why am I being invited to take part in TREC?

You are being invited because you have been diagnosed with a small rectal cancer that requires treatment. Your surgeon is not sure what the best treatment is for you, standard radical surgery or the new combined treatment using radiotherapy and a type of keyhole surgery. He/ she thinks that either of these treatments would be good options for you as would taking part in TREC. By taking part you would help research into which of these two treatments is best.

What does the standard treatment involve?

Standard radical surgery to remove the rectum is usually done through a cut in the abdomen (tummy). It can also be done as keyhole surgery through the tummy in some circumstances. It is normally possible to reconnect the remaining bowel to the anus once the rectum has been removed. This means that you can go to the toilet and pass faeces 'normally' through the anus. If the cancer happens to grow very close to the anus, then the rectum and anus must be removed together so that none of the cancer is left behind. The remaining bowel is then rerouted through the tummy wall and you must wear a bag (stoma) to collect faeces. Your doctor will be able to tell you before surgery if you are likely to need to wear a bag permanently. Patients will usually be in hospital for 4 to 10 days following surgery. We would expect full recovery to take up to 3 months. This may be quicker following keyhole surgery.

What are the benefits of standard treatment?

Standard treatment with radical surgery to remove the rectum has been used successfully to treat both small and large rectal cancers for many years and we know that it usually cures rectal cancer. We think that only 3 - 6 patients in every 100 treated by radical surgery will have their cancer come back. This means that at least 94 out of every 100 people treated in this way are likely to be cured of cancer.

What are the risks of standard treatment?

Like any major operation, radical surgery may result in serious side effects or rarely even death. The risk of death due to radical surgery is roughly 4 in every 100 operations. Your own level of risk depends upon your age and overall physical fitness. For example, in patients aged 75 - 85 years the risk of death can be as high as 15 out of every 100 cases.

One of the most serious complications after standard radical surgery is a leak of faeces from the bowel where it has been joined to the anus. More surgery is usually required to control this problem. This often involves rerouting the bowel through the tummy wall into a bag (stoma). Although we do our best to avoid leaks they remain quite common. Leaks complicate 5 - 15 out of every 100 operations. Your surgeon will be able to tell you about complication rates in your own local hospital.

Standard radical surgery can cause bowel control to change. More visits may be required per day before the bowel is empty. There may be less warning of the need to visit the toilet, leading some to stay indoors until they are sure their bowels have worked. Faeces may leak without warning, more

often at night. Large studies show that these problems are quite common after radical surgery, affecting approximately 40 out of every 100 people treated. In addition to this, nerves travelling through the pelvis close to the rectum on their way to the bladder and sexual organs may be inadvertently injured during radical surgery. This damage can lead to difficulty passing urine and impotence in men.

What does the new combined treatment with radiotherapy and local surgery involve?

Radiotherapy is given as an outpatient in five separate sessions over one week. We then wait for eight to ten weeks to allow time for the cancer to shrink or even disappear completely. A small 'keyhole' operation is then performed through the anus to remove the area affected by cancer. The rest of the rectum and anus that were not affected directly by the cancer are left alone. The operation is called transanal endoscopic microsurgery or transanal endoscopic operation depending on what brand of equipment your surgeon uses. These names are often shortened to TEMS or TEO. TEMS/TEO is performed under general anaesthetic and patients are normally allowed home the next day. Full recovery should take less than a week.

What are the benefits of the new treatment with radiotherapy and local surgery?

Many hundreds of patients with small cancers have already been treated with TEMS (but without radiotherapy) so we know that this operation is safe and only requires a short hospital stay. Recovery is also very quick. The risk of dying during the operation is small even for elderly patient's with other medical problems; perhaps 1 in 100 cases. The risk of other serious problems after surgery is also small. The bowels work normally after TEMS as do the bladder and sexual organs. TEMS on its own cures most patients with small rectal cancers but it is not as effective as radical surgery.

Radiotherapy has been used in thousands of patients to treat large rectal cancers before they are removed with radical surgery. Radiotherapy reduces the risk of these larger cancers coming back by more than a half. We think that it could be used to treat small cancers so that they can be removed safely through the anus using TEMS surgery. We hope that a combination of radiotherapy and TEMS will be about as effective a treatment as radical surgery for small rectal cancers but we can't be sure.

What are the risks of the new treatment with radiotherapy and local surgery?

The biggest risk with the new treatment is that it may not be as successful as radical surgery in preventing the cancer coming back. If the cancer does come back, it is likely to be harder to treat than it would be now. But, by combining radiotherapy and TEMS surgery, we hope that the risk of cancer returning will be low and close to that for standard radical surgery. As very few people have received this new combined treatment with radiotherapy and TEMS we can't be sure of this. One small study treated 30 patients in this way with good results and no unexpected problems. Once the cancer has been removed we will look at it under the microscope to decide whether radiotherapy worked well. If we are concerned that the cancer has not responded well to radiotherapy then we will recommend that you go on to have conventional radical surgery to remove the entire rectum within a period of one or two months.

We do not know if patients treated with radiotherapy and TEMS will go on to experience bowel problems. It is possible that treatment could cause some people to visit the toilet more often to pass faeces and there may be less warning of a need to visit the toilet. One or two years after radiotherapy, some people may suffer from inflammation of the bowel wall. This can cause bleeding from the bowel.

Do I have to take part?

No. Taking part in research is always voluntary. If you decide to take part you will be given this information sheet to keep, and will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part, then you don't have to give a reason why and no-one will think badly of you for not wishing to take part. Your surgeon will be happy to talk through alternative options.

What will happen to me if I agree to take part in TREC?

To begin with, all patients will be investigated with an MRI scan and an ultrasound scan of the rectum. These tests look closely at the rectum to make sure that the cancer is small and suitable for both treatments offered in the study.

If you decide to take part in **TREC** you will have the cancer treated by either:

Radical surgery to remove the rectum (as described above) or

A one-week course of radiotherapy followed by local surgery through the anus (8-10 weeks later).

If you receive radiotherapy followed by a local operation, you will be seen by a radiotherapy doctor to plan your treatment. Radiotherapy is given once a day for 5 days. You will be positioned lying on your front and asked to keep still for 10 minutes while the treatment is given. Afterwards you will be able to go home. Once radiotherapy has been completed you will see the surgeon to arrange a date for the cancer to be removed, 8-10 weeks later. The operation will be done under general anaesthetic. You will normally be able to go home the next day. As the cancer is removed through the anus there are no visible wounds or stitches to remove.

The surgeon will see you back in outpatients once the cancer has been examined in the laboratory. He/she will talk to you about how effective the radiotherapy was and whether you should consider having further surgery to remove the whole rectum.

Which of these treatments would I receive?

We ask that treatment is allocated at random by the **TREC** study office. We are advising this because it is the best way to allow a fair comparison to be made between the different treatments. Dividing people into treatment groups in this way is what is called a 'randomised clinical trial' and it is the standard and only reliable way of comparing different treatments. However, if you have a strong preference for one of the treatments, you would be able to discuss having it. Whatever treatment you receive, your progress would be followed up regularly.

Would taking part in TREC involve extra clinic visits or investigations?

Whether or not you take part in the **TREC** study, your progress will be followed up for at least five years. You will be reviewed in the outpatient clinic six weeks after discharge, then every three months for the first year. You will then be seen every six months for a further four years. You will have an MRI scan 3 months after surgery and then every year. As part of the **TREC** study, we would ask you to complete questionnaires before the start of treatment and then at 3, 6, 12, 24, 36, 48 and 60 months after surgery to tell us how healthy you feel and how well your bowels work.

With your consent, we would also like to take an extra blood sample before you start your treatment and also request your permission to retrieve from the hospital pathology laboratory some of the material from the biopsy taken to confirm you have cancer and from specimens of your cancer removed when you go on to have surgery. These samples will be labelled with a code number (not your name) and sent to a laboratory where some genetic tests will be done to find out whether measuring DNA or other chemicals from the tumour can predict which patients will benefit most from each treatment.

What are the possible benefits from taking part in TREC?

We are taking part in the TREC study because we hope that the new combination of radiotherapy followed by local surgery through the anus may result in fewer serious complications and better bowel function. People should spend less time in hospital, get back to normal activities much sooner and are perhaps less likely to end up with a permanent stoma bag. Unfortunately, we cannot be sure in advance that this treatment will have all of these benefits or that it will be as effective as standard radical surgery in preventing the cancer coming back – that is why we need to do this study. The main benefit from TREC will be that the information gained from the study will help doctors in the treatment of patients with a similar condition to yours in the future.

Part 2: Detailed information about the conduct of the study

What if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will discuss how this affects your care and your participation in the **TREC** study. Your research doctor might consider you should continue in the study or withdraw. Either way, he/she will explain the reasons and arrange for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form. If the study is stopped for any other reason, your doctor would, again, tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You can decide not to continue with study treatment at any time but, if you do, we would still like to follow up your progress and your data would remain on file and be included in the final study analysis unless you request that they should not be.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If the harm is due to someone's negligence, then you may have grounds for a legal action but you may have to pay for this. Whether or not you take part in the study, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you. Taking part in the study would not affect your legal rights.

Will my taking part be kept confidential?

If you decide to take part in **TREC**, all information collected about you during the course of the trial will be kept strictly confidential in the same way as all of your other medical records. Information about

your disease and progress will be sent by your doctors to the **TREC** Study Office at the University of Birmingham Clinical Trials Unit (BCTU), on paper and electronically, where it will be securely stored under the provisions of the 1998 Data Protection Act. Your GP, and the other doctors involved in your clinical care, will be notified of your participation in the **TREC** trial and kept informed of your progress. We may use national NHS records to track your progress, but otherwise all information about you and your treatment will remain confidential.

With your permission, your relevant medical records may be inspected by authorised individuals from the BCTU or the medical charity, Cancer Research UK (that is funding the study). They may also be looked at by the NHS Trust or regulatory authorities to check that the study is being carried out correctly.

What will happen to the results of the study?

Once the trial has finished, the results will be published in a medical journal so that others can benefit. We will also publicise the results on the trial's website www.TREC.bham.ac.uk. No individual patients will be identified in any publications. A copy of the published results of the trial will be sent to all patients who have participated in **TREC**. In line with clinical trial guidelines, at the end of the study, the data will need to be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made. Should you withdraw consent for your data to be used, it will be confidentially destroyed.

Who is organising and funding the research?

The **TREC** study was developed by the National Cancer Research Institute's Colorectal Cancer Clinical Studies Group, and is funded by the medical charity, Cancer Research UK. The study is coordinated by the Clinical Trials Unit at the University of Birmingham.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect the safety, rights, wellbeing and dignity of patients who take part. This study has been reviewed and approved by The Black Country Research Ethics Committee.

Where can I get further information?

If you have any further questions about your disease or clinical trials, please discuss them with your doctor. You may also find it helpful to contact CancerBACUP, an independent patient advisory group (freephone: 0800 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3DR; web site www.cancerbacup.org) or the CancerHelp website: <http://www.cancerhelp.org.uk/index.htm>

For any queries about the study or for further information please contact:

Name:

Tel No: **Position:**

The **TREC** study coordinating centre is located at the University of Birmingham Clinical Trials Unit, School of Cancer Sciences, Robert Aitken Institute, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Web address: www.bctu.bham.ac.uk;

e-mail: TREC@contacts.bham.ac.uk

Delete this line, then print on Trust headed paper

TREC- Transanal Endoscopic Microsurgery & radiotherapy in Early Rectal Cancer

Patient Consent Form - Version 2.0 2nd DECEMBER 2010

Please initial each box to indicate your consent

1. I confirm that I have read and understood the information sheet for the **TREC** study (version 2.0, dated 2/12/2010) and have had the opportunity to ask questions.
2. I understand that my participation in this study is voluntary and that, if I take part, I may withdraw at any time, without giving a reason, and without the standard of my medical care or my legal rights being affected.
3. I understand that a copy of this consent form and information about my progress will be supplied in confidence to the study coordinators at the University of Birmingham Clinical Trials Unit by my own doctors and by central registries for use in the **TREC** study.
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Clinical Trials Unit at the University of Birmingham, or from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
5. I understand that the study researchers may contact me by letter, telephone or email to remind me to complete the questionnaires or to ask me the questions over the telephone and that my address will be passed to the Birmingham CTU for the sole purpose of issuing the trial questionnaires.
6. I understand that my GP will be informed of my participation in the study and may be contacted to provide information about my progress, in confidence to the central organisers.
7. I understand that information held by the NHS and records maintained by The NHS Information Centre may be used to help contact me and provide information about my health status.
8. I agree to a blood sample being taken to be used for additional research **Yes** **No**
9. I agree to parts of the tissue removed for diagnostic purposes and at surgery being sent to the **TREC** laboratory and used for research, both within this study and in future related studies.
10. I understand that all information and samples collected will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results and that results from any additional research will not be recorded on my medical records. All studies using information and samples collected would require Research Ethics Committee approval.
11. I agree to take part in the **TREC** randomised comparison between standard surgery to remove the rectum and the new treatment of radiotherapy followed by delayed surgery to remove just the part of the rectum affected by the cancer. **Yes** **No**
12. If not, I agree to be treated with:

	Surgery to remove the rectum	<input type="checkbox"/>
	Radiotherapy & delayed surgery	<input type="checkbox"/>

Please note: Consent must be by a clinician. Clinician should not sign or print name for participant.

Name of Participant: Signature: Date:

Name of Clinician: Signature: Date:

Delete this line, then print on Trust headed paper

Dear Dr

Name: D.O.B:

NHS No:

Your patient, named above, has been diagnosed with early rectal cancer and has agreed to take part in the **TREC** pilot study.

The **TREC** study is a nationwide randomised controlled trial to assess whether short course radiotherapy followed 6-8 weeks later by local excision is better than the current standard of care for such patients, which is total mesorectal excision (TME). Radical surgery offers high rates of cure but is associated with substantial operative mortality and impaired bowel function. There are concerns that radical surgery may be over-treatment for early (screen detected) tumours.

The **TREC** trial is a multi-centre randomised controlled trial assessing short course preoperative radiotherapy plus delayed local excision, which we hope will be safer and functionally superior to radical surgery. However, we need a proper randomised evaluation of conservative surgery to confirm this and to make sure that the risk of cancer recurrence is not unacceptably increased.

The pilot phase of the **TREC** study is gathering data on the acceptability of randomisation between radical and conservative surgery, the efficacy of short-course radiotherapy in down sizing tumours and bowel function following different surgical approaches. Randomisation is encouraged but surgical choice can be elective if patient or surgeon considers one or other approach is definitely indicated.

TREC was developed by the National Cancer Research Institute's Colorectal Cancer Clinical Studies Group. The University of Birmingham Clinical Trials Unit are acting as coordinating centre. The study is funded by Cancer Research UK and receives no commercial support. The trial has been approved by <<Insert name of REC>> Multicentre Research Ethics Committee and the Local Research Ethics Committee at each participating centre.

Your patient has consented to take part in the **TREC** Trial and has been randomly allocated to:

Radical TME surgery SCPRT plus delayed local excision

I, or another member of the multi-disciplinary team responsible for your patient, will be updating you regularly on progress. If you have any queries about the patient's management, please feel free to contact me. If you require any further information about the **TREC** trial, it can be obtained from the **TREC** study office (see address below). Please file this letter in the patient's notes. I would appreciate being notified if they are no longer under your care.

Yours sincerely:

Name:

Position:

Further information about **TREC** is available from:

TREC Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Edgbaston, Birmingham B15 2TT Tel: 0121 415 9105 Fax: 0121 415 8871
Email: TREC@contacts.bham.ac.uk www.TREC.bham.ac.uk



TREC Trial – Randomisation Notepad



TREC – Randomisation notepad. Complete this form then telephone the Randomisation service: **0800 953 0274**

Part A – Identifying Details

Randomising centre:
 Patient's full name:
 NHS No:

Date of Randomisation: Day...../Month...../Year.....
 Randomising clinician:
 Date of Birth: Day...../Month...../Year.....
 Hospital number:

Part B – Histopathological assessment

- | | | | | |
|--|-----|--------------------------|----|-------------------------------------|
| 1. Does the patient have a biopsy proven adenocarcinoma? | Yes | <input type="checkbox"/> | No | <input checked="" type="checkbox"/> |
| 2. Has the patient already been subject to: | | | | |
| a. Submucosal excision? | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| b. Endoscopic polypectomy? | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |

*If shaded boxes are ticked, patient **not eligible** for TREC*

Part C – Radiological assessment

- | | | | | | | | | | |
|---|---------|----|--------------------------|----|-------------------------------------|----|-------------------------------------|-------|-------------------------------------|
| 3. MRI-defined TNM staging: | T-stage | TX | <input type="checkbox"/> | T1 | <input type="checkbox"/> | T2 | <input type="checkbox"/> | T3/T4 | <input checked="" type="checkbox"/> |
| | N-stage | NX | <input type="checkbox"/> | N0 | <input type="checkbox"/> | N1 | <input checked="" type="checkbox"/> | N2 | <input checked="" type="checkbox"/> |
| | M-stage | M0 | <input type="checkbox"/> | M1 | <input checked="" type="checkbox"/> | | | | |
| 4. Endorectal ultrasound defined TMN staging: | T-stage | T0 | <input type="checkbox"/> | T1 | <input type="checkbox"/> | T2 | <input type="checkbox"/> | T3/T4 | <input checked="" type="checkbox"/> |
| | N-stage | NX | <input type="checkbox"/> | N0 | <input type="checkbox"/> | N1 | <input checked="" type="checkbox"/> | N2 | <input checked="" type="checkbox"/> |
| | M-stage | M0 | <input type="checkbox"/> | M1 | <input checked="" type="checkbox"/> | | | | |
| 5. CT chest, abdomen and pelvis | M-stage | M0 | <input type="checkbox"/> | M1 | <input checked="" type="checkbox"/> | | | | |

Part D – Eligibility checklist

- | | | | | |
|---|-------|-------------------------------------|----|-------------------------------------|
| 6. Has the patient had previous pelvic radiotherapy? | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
| 7. If the patient is female – Is the patient pregnant or lactating? | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
| Does the patient have an adequate: | | | | |
| 8. Full blood count? | Yes | <input type="checkbox"/> | No | <input checked="" type="checkbox"/> |
| 9. Hepatobiliary function? | Yes | <input type="checkbox"/> | No | <input checked="" type="checkbox"/> |
| 10. Renal biochemistry? | Yes | <input type="checkbox"/> | No | <input checked="" type="checkbox"/> |
| 11. What is the patients Charlson status? | _____ | | | |
| 12. Has the patient given written informed consent? | Yes | <input type="checkbox"/> | No | <input checked="" type="checkbox"/> |
| 13. Which version of the consent form was used? | _____ | | | |
| 14. Name of the clinician taking written informed consent? | _____ | | | |

Part D – Randomisation – Treatment allocation

15. If allocated radical excision, which would be performed? APE Anterior Resection
- The patient has been randomised to receive:
- Radical Surgery Radiotherapy plus local excision
- TREC trial number**

Please return this form within 1 week of entry into the trial to: **TREC** Study Office, The University of Birmingham
 Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Appendix E - Administration of Short Course Preoperative Radiotherapy (SCPRT)

1. Irradiation technique

1.1 Dose specification

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 prescribed dose will be specified at the ICRU-50 reference point, which is located at or near the centre of the target volume at the intersection of the central ray of the beam or for more complex treatment arrangements at the centre of the target area(s). Dosimetry considerations and quality control require a display of isodose distributions in three transverse sections, i.e. at the central plane, one cranial and one caudal to the central plane. The isodose curve representing the 95% of the prescribed dose must encompass the entire PTV. The standard deviation of the dose within the PTV should be less than 1 to 2% of the prescribed dose provided that the mean dose (D_{mean}) and the median dose (D_{median}) are close to each other.

1.2 Planning technique

The use of 3-D conformal radiotherapy is recommended with simple coplanar or combination of coplanar and non-coplanar conformal deliverable fields. In accordance with the volume definitions, beam arrangements will be determined by 3D treatment planning software to produce the optimal conformal plan. 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.

1.3 External beam equipment

Radiation therapy must be delivered by photon radiation generated by a linear accelerator with effective photon energies ≥ 6 MV. Equipment of ≥ 10 MV is strongly recommended. Mixed beams are allowed with higher photon energy for the lateral beams compared to the posterior beam.

1.4 Missed fractions

Radiotherapy should start on a Monday and finish on a Friday. If an interruption of radiotherapy is unavoidable or radiotherapy cannot be started on a Monday (eg bank holiday), additional days of irradiation should be added after the weekend in order to complete the full dose of radiotherapy originally planned. Only one fraction is to be given per day.

1.5 Immobilization and bladder distension

The patient set-up must be accurate and reproducible. The patient should be treated in the prone position, which allows a better identification of the bony landmarks (e.g. sacrum). The use of immobilization devices to the head and legs are recommended. If the prone position is not feasible, the patient can be treated supine. In this situation, Styrofoam or a similar material may be used to lift the pelvis from the treatment couch in order to have a clear view on the bony structures and the posterior field edge. Measures should be taken to reduce the volume of small bowel in the treatment field if available, e.g. by using a belly board device or open tabletop device. The patient should be simulated and treated with a comfortably full bladder. This can be achieved by drinking three cups of water and waiting at least half an hour for a well-hydrated patient.

2. Simulation

2.1 3-D CT simulation

Prior to image acquisition, a radio-opaque marker should be placed at the anal verge by the supervising clinical oncologist or an appropriately trained radiotherapy radiographer. This serves as a reference point for the measured distance from the inferior border of the rectal tumour to the anal verge for the purpose of radiotherapy planning.

Three-dimensional CT simulation is preferred to 2-D orthogonal simulator planning. CT planning scan is performed in the treatment position for 3D treatment planning. CT slices of the whole pelvis should be taken with 3-5 mm separation. Intravenous contrast may be used to optimize the differentiation of soft tissue and vascular structures. Rectal contrast is recommended to allow for visualization of the tumour within the rectum. On all appropriate CT slices, the gross target volume (GTV) and the clinical target volume (CTV) should be outlined and displayed using beam's eye views.

2.2 Target volumes

General considerations

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. The relevant groups of pelvic lymph nodes at risk of microscopic metastases depend on the local tumour site, stage and grade.

Definitions

Gross tumour volume (GTV)

Gross tumour volume (GTV) is defined as all gross detectable sites of the primary tumour. It is important to realise that the primary tumour may not be visible on the planning CT scan. Therefore, the information used to localise the primary tumour have to be obtained from a combination of differing imaging techniques including MRI, CT, endorectal ultrasound as well as appropriate clinical findings from digital rectal examination (DRE) and rigid sigmoidoscopy and localised onto axial slices of a contrast enhanced CT planning scan.

Clinical target volume (CTV)

The CTV-1 is defined as the GTV plus the areas at risk for microscopic tumour extension. CTV-2 is defined as the loco-regional lymph nodes at risk for subclinical disease, which are not removed surgically. These include the mesorectal nodes, the presacral nodes and the internal iliac lymph nodes.

Mesorectal subsite (MS)

The lymph nodes within the mesorectum are usually the first site of lymphatic tumour spread and must be included in the CTV. Its circumferential boundary (mesorectal fascia) is best visualized on MRI and can often be identified on CT scan. The lower border of the mesorectal subsite is located at the level where the levator ani muscle inserts into the rectal wall. The upper border is located at the peritoneal fold, where the peritonealized rectum starts and bends anteriorly to form the recto-sigmoid. The inferior mesenteric artery (IMA) into the sigmoid artery and the upper rectal artery should be taken as the upper limit of the MS. Anteriorly, the mesorectal fascia coincides with Denonvillier's fascia, boarded by the posterior wall of the prostate/seminal vesicles/bladder in men and the posterior vaginal wall/uterus in women.

Around the dentate line, the mesorectal fascia matches the border of the levator ani muscle, which makes a funnel around the distal rectum. Above the dentate line, the piriform muscle bounds the fascia on both sides. Posteriorly, the MS lies alongside the posterior pelvic subsite.

Posterior pelvic subsite (PPS)

The PPS is at risk of lymph node involvement, independent of tumour location and should therefore be part of the CTV. The PPS corresponds mainly to the presacral space, a triangular strongly curved volume, which posteriorly faces the sacral concavity. Bounded anteriorly by the mesorectal fascia, it extends laterally towards the lateral borders of the sacrum where it encounters the posterior limit of the lateral lymph nodes (LLN). Its apex is directed caudally and corresponds to the coccyx, while the sacral promontory delineates its base. The anterior border that coincides with the posterior border of the mesorectal subsite is difficult to identify on CT

images and can be referred to MRI. An arbitrary maximal margin of +/- 1 cm ventrally from the sacral bone should be taken as the anterior border.

Inferior pelvic subsite (IPS)

If the IPS is not at risk for subclinical disease (tumour is located more than 6 cm above the anal margin), the external and internal sphincter with the surrounding ischiorectal fossa should not be included in the CTV.

Lymph node regions (LNR)

The LNRs at risk for microscopic disease depend on the level of the primary lesion. For tumours located in the upper part of the rectum (above the peritoneal reflection), the lymphatic spread is mainly in the upward direction along the inferior mesenteric nodes, while tumours in the middle and lower part of the rectum additionally drain in the lateral direction into the internal iliac nodes. All the lymph node regions at risk of microscopic spread should be included in the CTV as they are not removed surgically.

Planning target volume (PTV)

PTV is the volume that ensures coverage of the CTV taking into account systematic and random daily set up variation, changes over time in the patient geometry and internal movement that may occur when delivering a radical course of radiation. The most important factor is interfraction organ motion. PTV uses an added margin to the CTV (1 cm) for variations in tissue position, size, shape and also variations in patient position (ICRU Report 50, ICR 1993). Additional margins may be required based upon clinical judgment. Radiation field borders are designed to adequately cover the PTV. CT planning using 3D conformal treatment technique helps to adjust the field borders to ensure adequate coverage of the PTV.

Summary

The summary of this system is:

- CTV-1 (GTV expanded) = GTV expanded by 1 cm in all directions
- CTV-2 = mesorectal nodes, presacral nodes and internal iliac lymph nodes.
- PTV = (CTV1 + CTV2) + 1cm

GTV and CTV are anatomical concepts but PTV is a geometric construct, which includes both the CTV-1 (GTV expanded) and CTV-2 with a sufficient margin around to account for all the relevant intrafraction and interfraction uncertainties.

In general, the limits of CTV-2 are described below;

- **Posteriorly** the CTV-2 represents the pre-sacral fascia, i.e. the border is along the inner edge of the sacrum.
- **Anteriorly** the CTV-2 is represented by the most anterior aspect of the mesorectum seen on any of the CT slices within the plan or the most anterior aspect of the expanded GTV, whichever is the more anterior. In practice, in males the CTV-2 extends centrally to the prostate, seminal vesicles and bladder. In females the equivalent would be the vagina/cervix, uterus and bladder.
- **Inferiorly** the CTV-2 is contoured and will extend + 1cm beyond the expanded GTV.
- **Superiorly** the CTV-2 is represented by the S2/S3 junction, which can be found from the "scout" images produced at the time of the CT plan or 1cm of mesorectum beyond the expanded GTV, whichever is the larger.
- **Laterally** the CTV-2 should include the lateral pelvic nodes (obturator node). The CTV-2 is bounded by the internal obturator muscle.

However, there will be variations depending on the location of the tumour within the rectum;

Low Rectal Cancer (within 5cm of the anal verge)

- Inferiorly the proximal part of the external and internal sphincter with the surrounding ischiorectal fossa will usually be included.

Upper Rectal Cancer (between 10 and 15 cm of the anal verge)

- Anteriorly the CTV-2 may have to be extended further than in mid or lower rectal cancers to encompass the expanded GTV.
- Superiorly the CTV- may have to be extended further than in mid or lower rectal cancers to encompass the expanded GTV. However, efforts should be made not to extend the CTV-2 above the sacral promontory (L5/S1).

SUMMARY: The PTV is the GTV expanded + the CTV2 with an additional 1 cm, i.e. 1 cm beyond the pelvic sidewall, **e.g. PTV = the expanded GTV (GTV +1cm) + CTV2 + 1 cm.**

2.3 Treatment

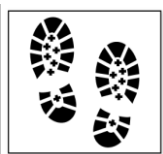
Radiation therapy should be delivered with effective photon energies >6 MV generated by a linear accelerator. Equipment of 10 MV or higher is recommended, as is the use of 3-D conformal radiotherapy. The field arrangements used can be either 3 or 4 fields at the Clinician's discretion. If a 3-field technique is used, mixed beams are allowed with higher photon energy for the lateral beams compared to the posterior beam. Patient set-up must be accurate and reproducible. The prone position is recommended because it allows a better identification of the bony landmarks (especially sacrum). If prone position is not feasible, the patient can be treated supine as described above.

Delineation of organs at risk (OAR): small bowel

At the time of CT planning small bowel contrast can be used to assist the exclusion of small bowel from the planning target volume. The small bowel should be contoured together with the peritoneum as one entity. The delineation should reach from the Douglas pouch up to the L5-S1 region.

Treatment verification

Isocentre position should be verified on the first treatment session. 3D imaging, such as CT cone beam imaging, is preferable if available. If not, electronic or film portal images should be taken on both PA or AP and a lateral field and compared to simulator films or digitally reconstructed radiographs (DRRs). Fields should be moved if they fall outside the locally accepted tolerance, usually 5mm. On line correction is preferred according to local protocol. If online correction is not available, off line correction must be undertaken before the second fraction and ideally confirmed on-line before delivery of the second fraction. Daily verification using EPIs or cone beam CT images may be undertaken according to local protocol.



TREC Trial: Radiotherapy Delivery Form

To be completed as soon as possible after completion of radiotherapy

Patient's Name:	Hospital:
NHS No:	Hospital No:
Clinician:	Date of Birth: Day...../Month...../Year.....
Date of Assessment: Day...../Month...../Year.....	TREC Trial No: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

Pelvic Radiotherapy details

Was radiotherapy given according to protocol?

Yes No

If 'no', please state and give reason(s) for deviation (e.g. delay, dose, method, stopped prematurely):

Date Radiotherapy Started: Day...../Month...../Year.....

Date Radiotherapy Completed: Day...../Month...../Year.....

Energy used (please tick all used)

6 MV 10MV 15 MV 18MV other, please state.....

Has a copy of the patient's plan(s) with TREC Trial No and D.O.B been sent to the trial centre?

Yes Date sent:/...../..... No Please state why.....

Verification Imaging

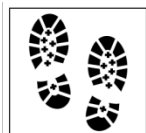
Verification imaging method(s) used: Film EPI CTCB 2DKV
 Other Please specify.....

	1	2	3	4	5
Fractions imaged <i>please tick</i>					
Any discrepancy(s) noted? <i>Please state in mm direction of displacement and/or rotation (after any on-line corrections)</i>	AP: LR: SI: Rotation(s):	AP: LR: SI: Rotation(s):	AP: LR: SI: Rotation(s):	AP: LR: SI: Rotation(s):	AP: LR: SI: Rotation(s):
Any action(s) taken from above imaging? <i>please state whether any corrections were subsequently applied and/or if treatment replanned</i>					

Form completed by: Date form completed: Day...../Month...../Year.....
 Sign Name: Tel No:

Thank you for completing this form

Please return to: TREC Study Office, The University of Birmingham Clinical Trials Unit
 FREEPOST RRRK-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham B15 2TT



TREC Trial: Radiotherapy Toxicity Form

To be completed at post-radiotherapy assessment- 2-3 weeks after completion of radiotherapy

Patient's Name: Hospital:
 NHS No: Hospital No:
 Clinician: Date of Birth: Day...../Month...../Year.....
 Date of assessment: Day...../Month...../Year..... TREC Trial No:

Worse toxicity experienced to date (CTCAE grade V4)

Nausea Diarrhoea Cystitis Anaemia Vomiting
 Skin reaction (Grade using Modified RTOG score)
 Other (specify and grade according to CTCAE V4):

WHO performance status

- 0 = Able to carry out all normal activity without restriction
 1 = Restricted in physically strenuous activity but ambulatory and able to carry out light work
 2 = Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
 3 = Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
 4 = Completely disabled; cannot carry on any self care; totally confined to bed or chair

Any Additional cancer treatment since last assessment: Yes (Please give details below) No

Radiotherapy: Date of 1st Cycle:/...../.....
 Further details:

Chemotherapy: Date of 1st Cycle:/...../..... Chemotherapy Regimen:
 Number of cycles:

Further details:

Surgery: Date of Surgery:/...../..... Type of Surgery:

Further details:

Other (give dates and details):

Quality of Life

Has Post-RT QoL form been completed? Yes No

If 'No', please give reasons:

Death

If patient has died, give date of death:/...../.....

Cause: Rectal Cancer Treatment Other, specify

Form Completed by: Date completed: Day...../Month...../Year.....

Sign Name: Tel No:

Thank you for completing this form

Please return to: TREC Study Office, The University of Birmingham Clinical Trials Unit
 FREEPOST RRRK-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham B15 2TT

CTCAE V4

Adverse Event	Grade1	Grade2	Grade3	Grade4	Grade5
Anaemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death

RTOG Modified skin reaction assessment scale

0	No change over baseline
1	Follicular, faint or dull erythema/ epilation/ dry desquamation/ decreased sweating
2a	Tender or bright erythema,
2b	Patchy moist desquamation, moderate oedema
3	Confluent, moist desquamation other than skin folds, pitting oedema
4	Ulceration, haemorrhage, necrosis



TREC Trial - Intraoperative Form



Please complete this form immediately after the patient has surgery (Radical or TEMS)

Patient's name: Hospital:
 NHS No: Hospital No:
 Surgeon: Date of Birth: Day...../Month...../Year.....

TREC No:

For ALL Patients

- Did the patient have surgery? Yes No
 If 'yes', date of surgery: Day...../Month...../Year.....
 If 'no', why not: _____
- What operation was performed?
 TEMS/TEO Anterior Resection APE Hartmans
- Was a temporary diverting stoma fashioned? Yes No
- What was the predominant tumour position? : Posterior
 Anterior
 Lateral
- Distance of lower tumour border from anal verge: _____(mm)
- Immediate Complications: _____

For Patients Receiving Local Treatment with TEMS/TEO

- What type of local excision was performed? :
 Full thickness with perirectal tissue: Yes No
 Full thickness with opening peritoneum: Yes No
 Partial and full thickness excision: Yes No
 - Was there complete surgical excision? : Yes No
 - What was the measured tumour diameter following excision (mm) once pinned out:
 Length: _____(mm)
 Width: _____(mm)
 - Was patient sutured? : Yes No
 - Was the tumour bed irrigated? : Yes No
 - Was there a **complete** clinical response to radiotherapy?
 Yes No
 - Was there any difficulty in localising the tumour following radiotherapy?
 Yes No
- If 'Yes' reasons why: _____

Form completed by: Date: Day...../Month...../Year.....

Sign Name: Tel no:

Please return this form to: TREC Study Office, The University of Birmingham Clinical Trials Unit,
 FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences,
 Birmingham B15 2TT



TREC Trial – SURGICAL REVIEW FORM

To be completed at 30 days post-surgery if still hospitalised



Patient's Name: Hospital:
 NHS No: Hospital Number:
 Surgeon: Date of Birth: Day...../Month...../Year.....
 *Date of Hospital discharge: Day...../Month...../Year..... TREC No: [][][][][]
 *Date fit for discharge, exclude time hospitalised for social reasons

1. Has the patient died: Yes No
 If 'Yes', what was the date of death: Day...../Month...../Year.....

Surgical Details

2. Did the patient have radical excision: Yes No
 If 'yes', which type of surgery was performed?
 Anterior resection
 Abdominoperineal excision
 Hartmann's
 3. Did the patient initially have a loop ileostomy: Yes No
 Date of Surgery: Day...../Month...../Year.....

Post-operative complications – please answer for all patients

1. Did the patient experience any complications that required or prolonged hospitalisation, were fatal or life-threatening? Yes No → If Yes, Date:/...../.....
If 'Yes' please complete SAE form

2. Did the patient experience:

- i) Urinary retention: Yes No → If Yes, Date:/...../.....
- ii) Bleeding in hospital: Yes No → If Yes, Date:/...../.....
Bleeding defined as i) Transfusion required, ii) Return to Theatre required (endoscopic or pen procedure), iii) GA or Sedation
- iii) Bleed readmission: Yes No → If Yes, Date:/...../.....
Bleeding defined as above
- iv) Stricture needing dilation: Yes No → If Yes, Date:/...../.....
 How was stricture dilated: Digital in clinic
 Endoscopy balloon
 GA with rigid dilators
 Other
 If 'Other', please specify: _____
- v) Stricture NO dilation: Yes No → If Yes, Date:/...../.....
Stricture defined as being unable to pass endoscope
- vi) Vaginal fistula: Yes No → If Yes, Date:/...../.....
- vii) Perineal fistula/abscess: Yes No → If Yes, Date:/...../.....
- viii) Intraoperative perforation or leak: Yes No → If Yes, Date:/...../.....
If 'Yes' was the perforation treated by laparotomy, laparoscopy or locally radiologically: _____
- x) Persistent post-operative pain: Yes No → If Yes, Date:/...../.....
- xi) Other: Yes No → If Yes, Date:/...../.....
 If 'Other', please specify: _____

3. Did the patient subsequently require a defunctioning stoma? Yes No
 If 'Yes', date of surgery: Day...../Month...../Year.....

4. Is conversion to radical surgery envisaged for the patient? Yes No
 If 'Yes', estimated date: Day...../Month...../Year.....

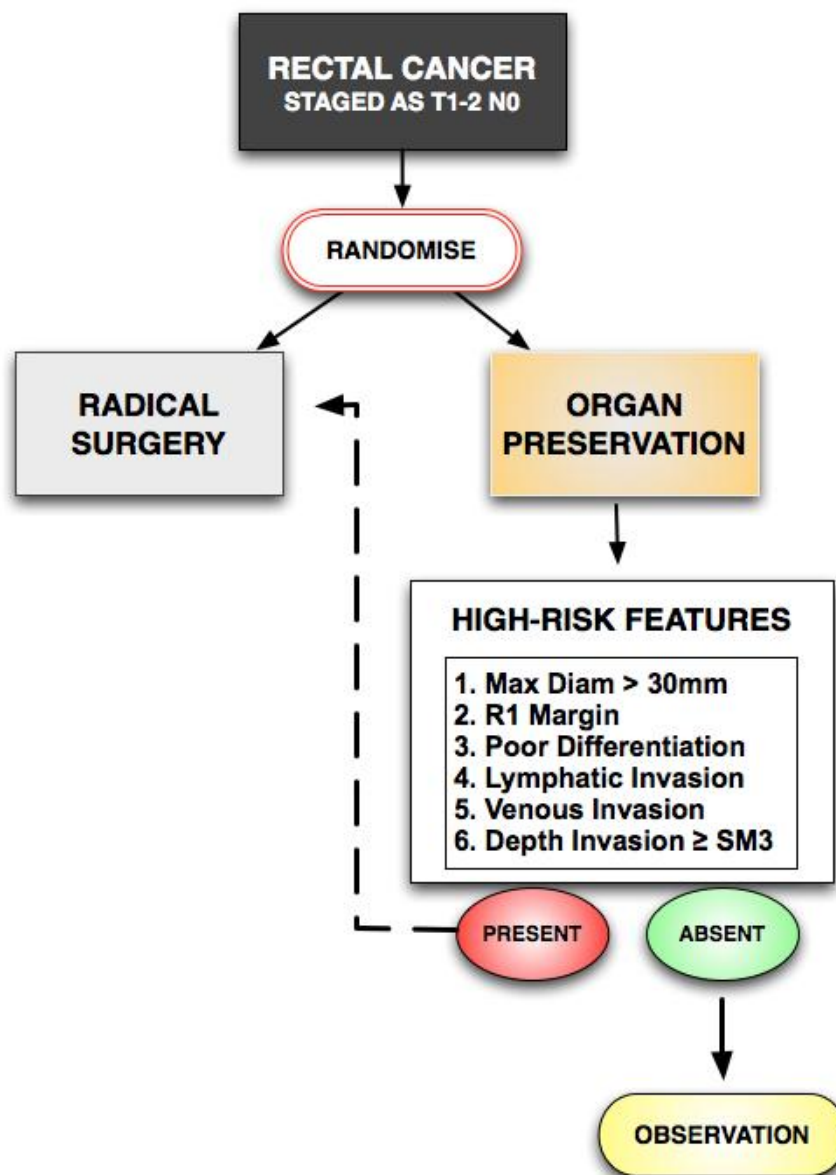
Form completed by: Date completed: Day...../Month...../Year.....
 Sign name: Telephone number:

Thank you for completing this form
 Please return to: TREC Study Office, The University of Birmingham Clinical Trials Unit
 FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham B15 2TT

PATHOLOGY PROTOCOL

Compiled by Professors Quirke and Warren

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 offered conversion to radical surgery. Unfortunately these high-risk features have been relatively poorly evaluated to date. They consequently form a rather subjective, and relatively non-specific group of markers. TREC will allow us to test some of these features against each other to improve the predictive value of histopathological assessment in this scenario. The high-risk features that we have selected are identified in the figure below.



In the section that follows high risk features are defined and the protocol for tissue handling, including cut up protocol described.

Tissue Handling

Local excisions are undertaken endoscopically or, in the case of early rectal tumours, under direct vision using TEMS or TEO. The majority of such tumours arise within pre-existing adenomas that may be pedunculated, sessile or flat, and the best pathological information is derived when lesions are excised in their entirety to include both the invasive and preinvasive components. Pedunculated lesions on a narrow stalk can be fixed intact, while sessile lesions should be pinned out, mucosal surface upwards, on a small piece of cork or other suitable material, taking pains to identify the narrow rim of surrounding normal tissue, before fixing intact, by placing (tissue down) into a container of formalin. Piecemeal removal of tumours, entirely acceptable for palliative resections, should be avoided because it precludes a reliable assessment of completeness of excision.

After fixation, pedunculated lesions may be bisected through the stalk if they measure <10mm; larger polyps are trimmed to leave a central section containing the intact stalk, and all fragments embedded for histology. It is recommended that at least three sections are taken from blocks containing the stalk. The margins of larger, sessile lesions should be identified with appropriate coloured markers (inks or gelatine) and the whole of the specimen transversely sectioned into 3mm slices and submitted for histology in sequentially labelled cassettes. In cases where the margin of normal tissue is less than 3mm, a 10mm slice containing the relevant margin should be made and further sectioned at right angles. It can be helpful to embed the slices in agar at the time of cut up. This ensures maintenance of good orientation of both the deep resection margin and the mucosal resection margin. This also enables easier and possibly more accurate measurement of the depth of tumour invasion and the distance between the deepest extension of the tumour and the deep margin of the specimen.

Central review of slides

All H&E slides will be sent centrally for scanning and return within 30 days. Central review will be undertaken either by Professor Quirke or Professor Warren using electronic images and a number of additional studies performed. One block of cancer and one of normal mucosa should be submitted for tissue microarray preparation. Where there is more than one block of cancer we would like to hold onto the blocks but where there is not we will return the blocks with the slides.

Definition of invasion

We recommend the use of the WHO definition (1989; 2000) of an adenocarcinoma of:

- **An invasion of neoplastic cells through the muscularis mucosae into the submucosa.**

This definition disallows the diagnosis of intramucosal carcinoma or carcinoma in situ and this should be considered as mucosal high-grade neoplasia according to the WHO classification and the revised Vienna classification.

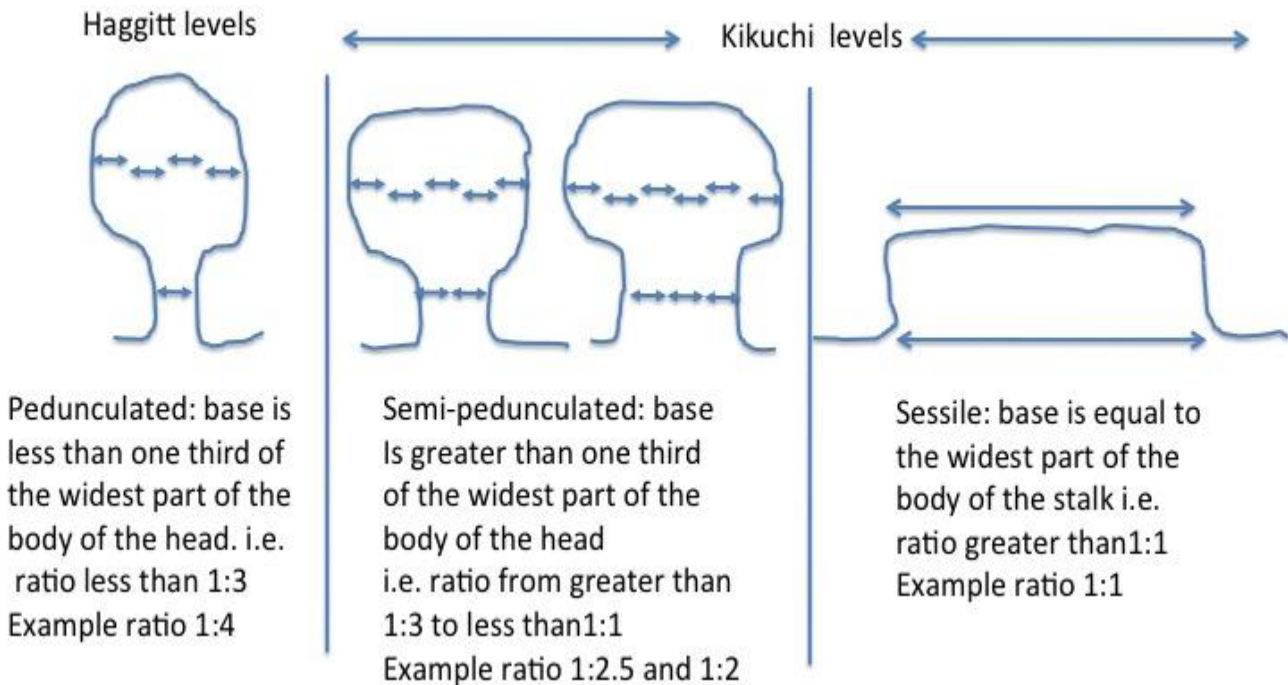
Tumour Shape

At endoscopy a polypoid neoplastic lesion will protrude above the surrounding surface. In the operative specimen, the height of the lesion is more than double the thickness of the adjacent mucosa. The lesion should be classified as sessile, sub-pedunculated or pedunculated. In pedunculated polyps, the base is narrow; in sessile polyps, the base and the top of the lesion have the same diameter. Intermediate and broad-based forms are called sub-pedunculated; they should be assessed as sessile polyps.

Some difficulty may be experienced when differentiating pedunculated versus sub-pedunculated polyps. A rule of thumb should be applied that if the width of the base is less than one third of the maximum width of the lesion then it is classified as a pedunculated lesion.

- (i) Pedunculated - *Width of base < 33% of width of body.*
- (ii) Sessile - *width of base = widest part of body.*
- (iii) Sub-pedunculated - *Width base > 33% (but not equal to) width body.*

Examples of Pedunculated, Semi-pedunculated and Sessile lesions



Assessment of High Risk Features

(1) Size

Maximum diameter $\leq 30\text{mm}$. This will be measured clinically but should also be accurately measured by the pathologist on the slide(s) as endoscopic estimates have been described to exaggerate the size of lesions. Since these will be rectal cancers this should be clinically less of a problem but the size of the cancer vs. adenoma should be determined.

(2) Margin involved by:

- (i) **Cancer** - defined as tumour within 1 mm or less of any surgically resected margin.
- (ii) **Adenoma** - defined as adenoma in the mucosal margin.

(3) Poor differentiation

Differentiation should be judged by the WHO classification however the groups should be merged into only two; poor and other. Well/moderately differentiated should be grouped together. Poorly differentiated and undifferentiated should be grouped together.

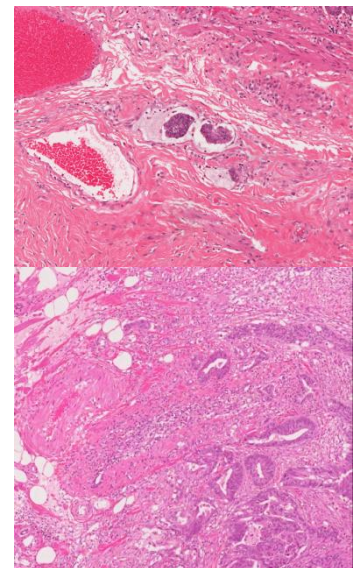
When a carcinoma has heterogeneity in differentiation, grading should be based on the least differentiated component, not including the leading front of invasion. Small foci of apparent poor differentiation are common at the advancing edge of the tumours, but this feature is insufficient to classify the tumour as poorly differentiated.

(4) Lymphatic invasion

Definition: When the tumour is identified in an endothelial lined space devoid of mural smooth muscle and elastic fibres

(5) Venous invasion

Definition: On H&E stain: Tumour within a round or ovoid endothelial lined channel with a smooth muscle wall. On Verhoff elastic stains: Tumour within a round or ovoid vessel like structure containing elastic tissue fibres in an orderly concentric fashion. Where the tumour obliterates the vascular lumen: Presence of organised smooth muscle fibres of the residual vascular media around a tumour deposit, in proximity of neurovascular bundles and/or following the path of neurovascular bundles.

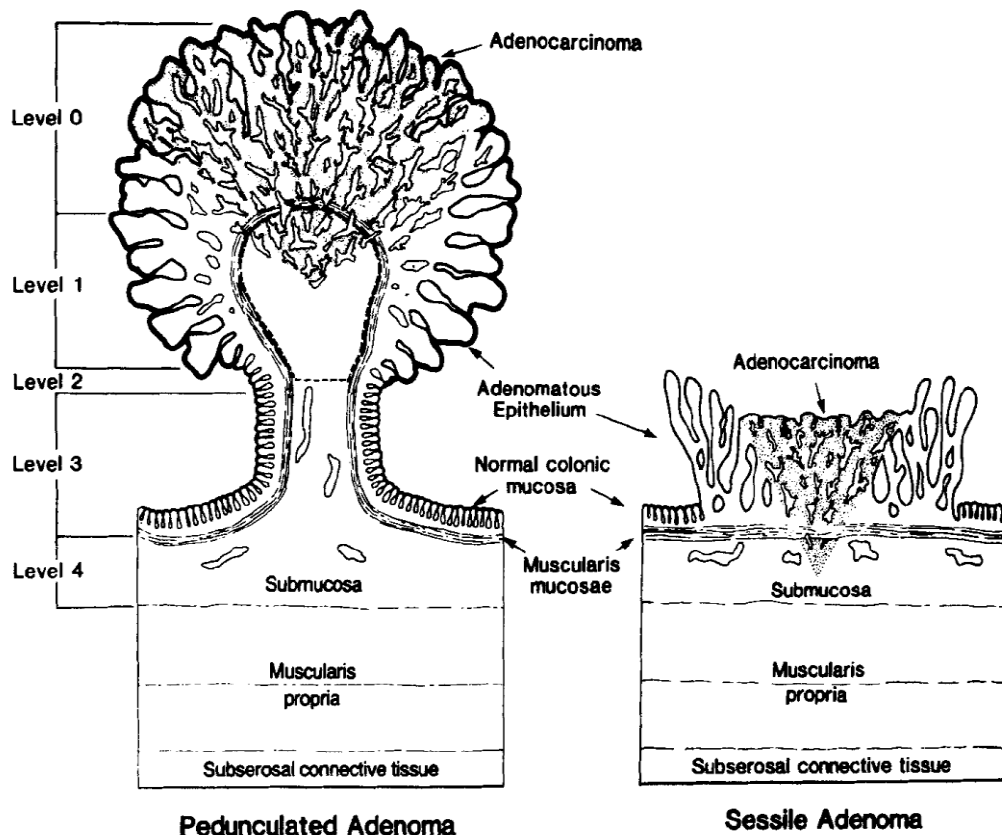


(6) Invasion and sub staging of pT1

Where a lesion is clearly pedunculated (polypoid) then Haggitt levels should be used. Where the lesion is sessile or sub-pedunculated the Kikuchi levels should be used to define a high-risk lesion on the basis of depth. Haggitt level 4 or Kikuchi Sm3 define a high-risk lesion.

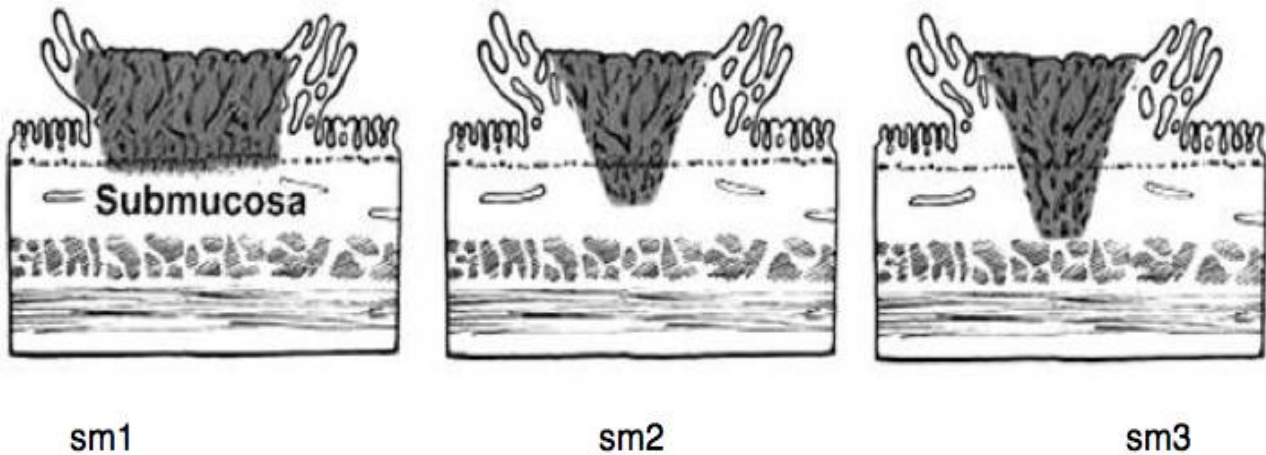
(i) Haggitt levels

- Level 1: Invasion of submucosa but limited to the head of the polyp.
- Level 2: Invasion extending into the neck of the polyp.
- Level 3: Invasion into any part of the stalk.
- Level 4: Invasion beyond the stalk but above the muscularis propria.



(ii) Kikuchi depth

Invasion by carcinoma of the submucosa (pT1) is divided by depth into the superficial third (pT1 Sm1), the middle third (pT1 Sm2) or the deepest third (pT1 Sm3). Lymph node involvement has been reported to be 2%, 8% and 23% depending on level.



Additional Histopathological Parameters to be measured

a. Depth of tumour Invasion

This should be accurately measured by the Vernier scale. The actual depth measured at right angles from where the pathologist estimates that the muscularis mucosae is or would have been if the tumour has destroyed it.

b. Tumour regression grade (TRG) after SCPRT

This should be graded into:

- Complete response:** No tumour cells visible despite embedding the entirety of the tumour and sectioning at three levels.
- Good response:** Few tumour cells that are hard to find and can only be seen microscopically.
- Moderate response:** Fibrosis is the predominant feature with easily visible tumour cells present.
- Mild response:** Easily found tumour with some fibrosis and tumour response.
- No response:** No evidence of tumour damage.

<p>complete response</p> <p>good response</p> <p>moderate response</p> <p>poor response</p> <p>no response</p>		<p>TRG 1 No residual cancer</p> <p>TRG 2 Rare residual cancer cells</p> <p>TRG 3 Fibrosis outgrowing residual cancer</p> <p>TRG 4 Residual cancer outgrowing fibrosis</p> <p>TRG 5 Absence of regressive changes</p>	
--	--	--	--

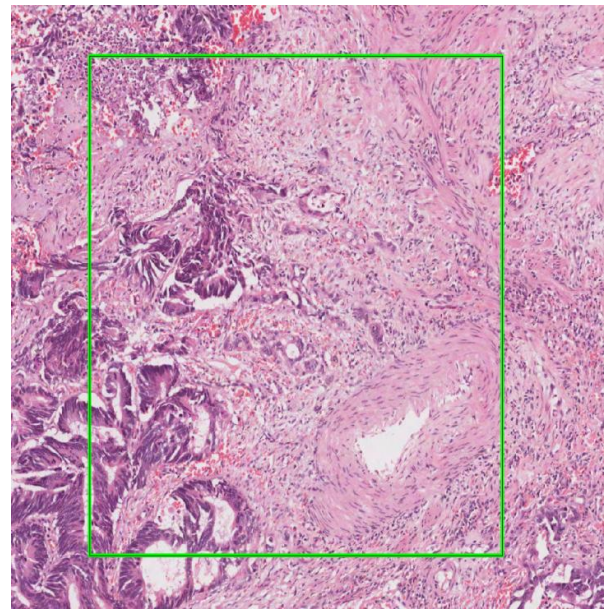
Other factors that will be assessed centrally:

c. Tumour budding

Tumour cell budding, the presence of small islands or single infiltrating tumour cells at the front of tumour invasion have been described as an unfavourable prognostic factor if present in a marked degree in the Japanese literature (Sakuragi et al 2003; Ueno et al 2004; Masaki et al 2006). It can be divided into slight, moderate and marked or assessed as present/absent (Deinlen et al 2003; Wang et al 2005). We have chosen a definition of present or absent (Kitajima et al 2004).

Definition: Tumour budding is defined as an isolated single cancer cell or a cluster composed of fewer than 5 cancer cells. After choosing one field where budding is the most intensive, a budding count should be made in the field measuring 0.785 mm² using a 20x objective lens.

A field with 5 or more buds should be reported as positive. This feature does not define the case as high risk and is for research purposes only.



d. Measurements

Measurements have been reported as more accurate for assessment of invasion. We have decided that the full range of Japanese measurements will be measured electronically on the digital slides to ensure consistency.

References

Deinlein P, Reilbach U, Stolte M, Vieth M. Risk factors for lymphatic metastasis from pT1 colorectal adenocarcinoma *Pathologie* 2003 24;387-93.

Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985; 89: 328-36.

Hassan C, Zullo A, Risio M, et al. Histologic risk factors and clinical outcome in colorectal malignant polyp: a pooled-data analysis. *Dis Colon Rectum* 2005; 48(8):1588-1596.

Kitajima K et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol* 2004; 39:534–543

Masaki T, Matsuoka H, Sugiyama M, et al. Actual number of tumor budding as a new tool for the individualization of treatment of T1 colorectal carcinomas. *J Gastroenterol Hepatol* 2006; 21(7):1115-1121.

Minsky BD et al. Resectable adenocarcinoma of the rectosigmoid and rectum. The influence of blood vessel invasion. *Cancer* 61: 1417-1424, 1988

Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002; 45: 200-206.

Okuyama T, Oya M, Ishikawa H. Budding as a risk factor for lymph node metastasis in pT1 or pT2 well-differentiated colorectal adenocarcinoma. *Dis Colon Rectum* 2002; 45(5):628-634.

Quirke P, Williams GT. *Minimum Dataset for Colorectal Cancer Histopathology Reports* 2007 London, Royal College of Pathologists.

Sakuragi M, Togashi K, Konishi F, et al. Predictive factors for lymph node metastasis in T1 stage colorectal carcinomas. *Dis Colon Rectum* 2003; 46(12): 1626-1632.

Ueno H, Mochizuki H, Hashiguchi Y, et al Risk Factors for an Adverse Outcome in Early Invasive Colorectal Carcinoma *Gastroenterology* 2004;127:385–394.

Volk EE, Goldblum JR, Petra RE, et al. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology* 1995; 109: 1801-1807.

Wang H-S, Liang W-Y, Lin T-C, et al. Curative resection of T1 colorectal carcinoma: risk of lymph node metastasis and long-term prognosis. *Dis Colon Rectum* 48: 1182-1192, 2005.

World Health Organization classification of Tumours. Hamilton S R, Aaltonen L A Pathology and genetics of tumours of the digestive system. Carcinoma of the colon and rectum. Vol 2. IARC Press, Lyon, 2000. 105-119.

World Health Organization International Histological Classification of Tumours. Jass JR, Sobin LH (Eds.) *Histological Typing of Intestinal Tumours. Second Edition.* Springer-Verlag, Berlin 1989. pp 30.



TREC Trial - Proforma for Local Excision Specimens



Patient's Name: Hospital:
 Surgeon: Hospital No:
 Pathologist: Report No:
 Date of assessment: Day...../Month...../Year..... TREC Trial No: [][][][][]

Specimen Type
 Endoscopic Mucosal Resection Polypectomy
 Transanal Endoscopic Microsurgical (TEM) Excision Other
 Comments:

Gross Description
 Site of Tumour:
 Maximum Tumour diameter (if known): (mm)

Shape
 Pedunculated Sub pedunculated
 Sessile
Tumour type
 Adenocarcinoma: Yes No
 If No, Other
Differentiation
 Well / Moderate Poor
Local invasion
 Confined to submucosa (pT1)
 Into muscularis propria (pT2)
 Beyond muscularis propria (pT3)
For pT1 tumours:
 Max thickness of invasive tumour from muscularis mucosae: (mm)
 Max width of adenocarcinoma: (mm)
Haggitt level (pedunculated tumours)
 1 2 3 4
Kikuchi Level
 Sm1 Sm2 Sm3
Lymphatic invasion:
 None Present
Vascular invasion
 None Present
Background adenoma:
 Yes No

Margins
 Not involved
 Involved by adenoma (direct – 0mm)
 Deep margin involved by carcinoma (≤1mm)
 Peripheral margin involved by carcinoma (≤1mm)
 Histological measurement from carcinoma to nearest deep excision margin: (mm)
Evidence of tumour response
 Complete response
 Good response
 Moderate response
 Mild response
 No response
Summary
 Excision of adenoma at all margins
 Yes No
 Excision of carcinoma at all margins (>1mm)
 Yes No
 Poor differentiation
 Yes No
 Depth of invasion
 Sm1 Sm2 Sm3 pT2
 Presence of lymphatic invasion
 Yes No
 Presence of vascular invasion
 Yes No
TNM (v5) pT..... pN..... pM.....
SNOMED codes: T..... / M.....

Print Name: **Date:** Day...../Month...../Year.....
Signature:



Health Questionnaire

*(English version for the UK)
(Validated for use in Eire)*

© EuroQoL Group 1990

Patient Forename:..... Patient Surname:

Date of Birth:/...../..... Hospital:.....
 dd mmm yyyy

TREC Trial No:..... Todays date:/...../.....
 dd mmm yyyy

EuroQol Questionnaire (EQ-5D)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

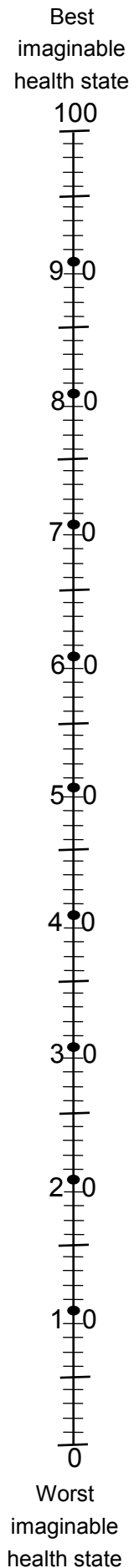
Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**





EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1	Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2	Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3	Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4	Do you need to stay in bed or a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

		Not at All	A Little	Quite a Bit	Very Much
During the past week:					
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4



EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
During the past week:	Not at All	A Little	Quite a Bit	Very Much
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

During the past week:

**Not at
All A
Little Quite
a Bit Very
Much**

Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue the form below:

49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems carling for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:

49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:

**Not at
All A
Little Quite
a Bit Very
Much**

For men only:

56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection	1	2	3	4

COloRectal Functional Outcome (COREFO) Questionnaire

Dear patient,

Please could you kindly fill this questionnaire in while waiting to be seen in clinic or while waiting for your operation. Please try to answer every question, with the answer that fits best. The answers will remain **CONFIDENTIAL**. They will be used to assess your quality of life, functional outcome (bowel function – urinary function – sexual function) severity and range of your symptoms and the influence of treatment on your symptoms. Thus you may be asked to fill out another questionnaire after treatment.

Patient Forename:..... Patient Surname:

Date of Birth:/...../..... Hospital:.....
dd mmm yyyy

TREC Trial No:..... Todays date:/...../.....
dd mmm yyyy

Attention: These questions relate to **the last two weeks!**

1. How many bowel movements have you had during the day? (average per day)

0-1 2-4 5-7 8-10 11 times or more

2. How many bowel movements have you had during the night? (average per night)

0 1-2 3-4 5-6 7 times or more

3. In case you needed to go urgently, did you have trouble stopping your bowel movement for longer than fifteen minutes?

No, never	<input type="checkbox"/>	Yes, less than once a week	<input type="checkbox"/>
Yes, 1-2 days per week	<input type="checkbox"/>	Yes, 3-5 days per week	<input type="checkbox"/>
Yes, 6-7 days per week	<input type="checkbox"/>		

4. Have you had a false alarm? (= a need to go without a bowel movement)?

No, never	<input type="checkbox"/>	Yes, less than once a week	<input type="checkbox"/>
Yes, 1-2 days per week	<input type="checkbox"/>	Yes, 3-5 days per week	<input type="checkbox"/>
Yes, 6-7 days per week	<input type="checkbox"/>		

5. Have you had pain during your bowel movements?

No, never	<input type="checkbox"/>	Yes, less than once a week	<input type="checkbox"/>
Yes, 1-2 days per week	<input type="checkbox"/>	Yes, 3-5 days per week	<input type="checkbox"/>
Yes, 6-7 days per week	<input type="checkbox"/>		

6. Have you experienced blood loss during your bowel movements?

No, never	<input type="checkbox"/>	Yes, less than once a week	<input type="checkbox"/>
Yes, 1-2 days per week	<input type="checkbox"/>	Yes, 3-5 days per week	<input type="checkbox"/>
Yes, 6-7 days per week	<input type="checkbox"/>		

Attention: These questions relate to **the last two weeks!**

7. Have you unintentionally passed wind?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

8. Have you unintentionally passed **liquid** stools during the day?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

9. Have you unintentionally passed **liquid** stools during the night?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

10. Have you unintentionally passed **solid** stools during the day?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

11. Have you unintentionally passed **solid** stools during the night?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

Attention: These questions relate to **the last two weeks!**

12. Have you had a smear of faeces in your underwear during the day?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

13. Have you had a smear of faeces in your underwear, pyjamas or nightgown at the end of the night?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

14. Was it difficult to distinguish between passing wind and a bowel movement?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

15. When you went to the toilet, did your bowel movement require more than 15 minutes?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

16. Did you have the idea that your bowels were not empty after your bowel movement?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

Attention: These questions relate to **the last two weeks!**

17. After you had a bowel movement, did you have to return to the toilet within one hour for a bowel movement?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

18. Have you used medicines to thicken your stools?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

19. Have you used medicines to make your stools thinner?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

20. Have you eaten certain foods **on purpose** to make your stools thicker or thinner?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

21. Have you **purposely** avoided certain foods to prevent your stools becoming loose or hard?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

Attention: These questions relate to **the last two weeks!**

22. Have you had irritated skin around your anus?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

23. Have you used something to protect your underwear, such as sanitary towels, panty liners or nappies?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

24. Did you adjust your activities to the availability of a toilet?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

25. Were you limited in your daily activities (e.g. work or house work) due to problems with your bowel movements?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

26. Were you limited in your social activities (e.g. family visits, visits to the theatre, or eating out) due to problems with your bowel movements?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

Attention: These questions relate to **the last two weeks!**

27. Were you limited in your sexual activities (with or without sexual intercourse) due to problems with your bowel movements?

- | | | | |
|------------------------|--------------------------|----------------------------|--------------------------|
| No, never | <input type="checkbox"/> | Yes, less than once a week | <input type="checkbox"/> |
| Yes, 1-2 days per week | <input type="checkbox"/> | Yes, 3-5 days per week | <input type="checkbox"/> |
| Yes, 6-7 days per week | <input type="checkbox"/> | | |

Questionnaire on Urinary Dysfunction (IPSS)**28. Incomplete emptying**

Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?

Not at all	<input type="checkbox"/>	Less than 1 time in 5	<input type="checkbox"/>	Less than half the time	<input type="checkbox"/>
About half the time	<input type="checkbox"/>	More than half the time	<input type="checkbox"/>	Almost always	<input type="checkbox"/>

29. Frequency

Over the past month, how often have you had to urinate again less than two hours after you finished urinating?

Not at all	<input type="checkbox"/>	Less than 1 time in 5	<input type="checkbox"/>	Less than half the time	<input type="checkbox"/>
About half the time	<input type="checkbox"/>	More than half the time	<input type="checkbox"/>	Almost always	<input type="checkbox"/>

30. Intermittency

Over the past month, how often have you found you stopped and started again several times when you urinated?

Not at all	<input type="checkbox"/>	Less than 1 time in 5	<input type="checkbox"/>	Less than half the time	<input type="checkbox"/>
About half the time	<input type="checkbox"/>	More than half the time	<input type="checkbox"/>	Almost always	<input type="checkbox"/>

31. Urgency

Over the last month, how difficult have you found it to postpone urination?

Not at all	<input type="checkbox"/>	Less than 1 time in 5	<input type="checkbox"/>	Less than half the time	<input type="checkbox"/>
About half the time	<input type="checkbox"/>	More than half the time	<input type="checkbox"/>	Almost always	<input type="checkbox"/>

32. Weak stream

Over the past month, how often have you had a weak urinary stream?

Not at all	<input type="checkbox"/>	Less than 1 time in 5	<input type="checkbox"/>	Less than half the time	<input type="checkbox"/>
About half the time	<input type="checkbox"/>	More than half the time	<input type="checkbox"/>	Almost always	<input type="checkbox"/>

33. Straining

Over the past month, how often have you had to push or strain to begin urination?

Not at all	<input type="checkbox"/>	Less than 1 time in 5	<input type="checkbox"/>	Less than half the time	<input type="checkbox"/>
About half the time	<input type="checkbox"/>	More than half the time	<input type="checkbox"/>	Almost always	<input type="checkbox"/>

34. Nocturia

Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?

None	<input type="checkbox"/>	1 time	<input type="checkbox"/>	2 times	<input type="checkbox"/>	3 times	<input type="checkbox"/>	4 times	<input type="checkbox"/>	5 times or more	<input type="checkbox"/>
------	--------------------------	--------	--------------------------	---------	--------------------------	---------	--------------------------	---------	--------------------------	-----------------	--------------------------

35. Quality of life due to urinary symptoms

If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?

Delighted	<input type="checkbox"/>	Pleased	<input type="checkbox"/>	Mostly satisfied	<input type="checkbox"/>
Mixed – equally satisfied and dissatisfied	<input type="checkbox"/>			Mostly dissatisfied	<input type="checkbox"/>
Unhappy	<input type="checkbox"/>	Terrible	<input type="checkbox"/>		

PLEASE ANSWER THE FOLLOWING SECTION IF YOU ARE FEMALE ONLY

The McCoy Female sexuality questionnaire

The following questions will be on your sexual function

Please circle the number from 1 to 7 which most closely corresponds to your experience during the past 30 days. Your response will be kept completely confidential.

1. Are you satisfied with your present frequency of sexual activity ?

Extremely Uns satisfied			neither satisfied, nor unsatisfied			extremely satisfied
1	2	3	4	5	6	7

2. How many times a day have you had sexual thoughts or fantasies during the last month?

None of the time		once a week		once a day		> 10 times a day
1	2	3	4	5	6	7

3. How enjoyable is sex for you?

Not at all enjoyable			Moderately enjoyable			Very enjoyable
1	2	3	4	5	6	7

4. How often during sex do you feel aroused or excited (for instance, increased heart beat/flushing/vaginal wetness/heavy breathing)

None of the time			About half of the time			Every time
1	2	3	4	5	6	7

5. How often do you have an orgasm during sex?

None of the time

About half of the time

Every time

1	2	3	4	5	6	7
---	---	---	---	---	---	---

6. How often do you suffer from lack of vaginal lubrication (wetness) during sex?

None of the time

About half of the time

Every time

1	2	3	4	5	6	7
---	---	---	---	---	---	---

7. How often do you suffer from pain during intercourse?

None of the time

About half of the time

Every time

1	2	3	4	5	6	7
---	---	---	---	---	---	---

This is the end of the questionnaire. Thank you for your time and patience.

PLEASE ANSWER THE FOLLOWING SECTION IF YOU ARE MALE ONLY

**The following questions will be on your sexual function.
Your response will be kept completely confidential.**

Please choose the appropriate column for each question about your sexual abilities over the past 4 weeks.

1. How do you rate your confidence that you could get and keep an erection?

Very low Low Moderate High Very high

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?

Never or almost never A few times Sometimes Most times
Almost always or always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Never or almost never A few times Sometimes Most times
Almost always or always

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Extremely difficult Very difficult Difficult Slightly difficult
Not difficult

5. When you attempted sexual intercourse, how often was it satisfactory for you?

Never or almost never A few times Sometimes Most times
Almost always or always

This is the end of the questionnaire. Thank you for your time and patience.



Serious Adverse Event form

Please **report immediately** any **SERIOUS ADVERSE EVENTS** (see protocol page 15 for definition) by completing all of the details below and faxing this form to the TREC Trial Office on **+44 121 415 8871**. Please also complete the SAE form if the patient dies of any cause other than colorectal cancer.

Patient's Initials: _____ Date of Birth: ____/____/____
 NHS No: _____ Hospital No: _____ **TREC** No:
 Responsible Clinician: _____ Hospital: _____

SAE description

Is this an initial or follow up report? Initial Follow up
 Is this the final report? Y N

Reason for reporting

Death? Y N Date of death ____/____/____
 Life threatening event? Y N
 In-patient hospitalisation or prolongation of existing hospitalization? Y N If yes, no of days? _____
 Persistent or significant disability/incapacity? Y N
 Other pertinent reason for reporting, e.g. new primary cancer? Y N
 If other, please specify: _____

Date event started: ____/____/____ Date event ceased: ____/____/____
 Details of adverse event (please attach copies of relevant reports): _____

Trial treatment

Is SAE related to radiotherapy or surgery? Radiotherapy Surgery
 What was the date of surgery? ____/____/____

If SAE is considered to be related to surgery or radiotherapy please assess causality (use codes given below): _____

This section must be completed by a clinician

Date of last treatment (surgery or radiotherapy)	If radiotherapy, date radiotherapy completed	If radiotherapy, Energy used (MV)	Causality assessment (use codes given below)

Causality assessment codes:

- 1 Probably unrelated to treatment
- 2 Possibly related to treatment
- 3 Probably related to treatment
- 4 Definitely related to treatment

Please give reasons if you consider the event to be treatment related: _____

Appendix O: Serious Adverse Event Form

Was the patient disease-free at the time of the event?

Yes No (residual disease) No (pre surgery) No (recurrent disease) Date of recurrence: ____/____/____

What was the outcome of the SAE?

Fatal Recovered Continuing

Signature of Person Reporting: _____

Date: ____/____/____

You must have signed the site
Delegation log

Name: _____

Position: _____

Telephone number: _____

Signature of Investigator: _____

Date: ____/____/____

If not completed by Investigator

SAE Reporting – BCTU USE ONLY

SAE reference number: _____

Date reported to BCTU: ____/____/____

Date reported to CI: ____/____/____

Date reply received from CI: ____/____/____

CI comments:

Date due to be reported to MREC: ____/____/____

When you have faxed the form, please then send (with copies of any relevant reports) to the TREC Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham B15

2TT

TREC TRIAL: ANNUAL FOLLOW-UP

PLEASE COMPLETE AND RETURN THIS FORM PROMPTLY

N.B. Please give details of any important protocol deviations, serious toxicity (requiring hospitalisation), cause of death, change of follow-up doctor, etc. in the COMMENTS field.

Patient Details	Date of surgery	Has the patient had at 12 months:	Has the patient had a recurrence of the disease?	Has the patient <i>died</i> ?	If patient is <i>alive</i> , approx date last seen:	COMMENTS: (See above)
Name: _____ DoB: __/__/____ Hospital No: _____ Date randomised: __/__/____ TREC trial no: _____	__/__/____ dd mmm yyyy	MRI: Yes <input type="checkbox"/> No <input type="checkbox"/> CT: Yes <input type="checkbox"/> No <input type="checkbox"/> Flexi sigmoid: Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/> Date: __/__/____ dd mmm yyyy Site: _____	Yes <input type="checkbox"/> No <input type="checkbox"/> Date of death: __/__/____ dd mmm yyyy	__/__/____ dd mmm yyyy	
Name: _____ DoB: __/__/____ Hospital No: _____ Date randomised: __/__/____ TREC trial no: _____	__/__/____ dd mmm yyyy	MRI: Yes <input type="checkbox"/> No <input type="checkbox"/> CT: Yes <input type="checkbox"/> No <input type="checkbox"/> Flexi sigmoid: Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/> Date: __/__/____ dd mmm yyyy Site: _____	Yes <input type="checkbox"/> No <input type="checkbox"/> Date of death: __/__/____ dd mmm yyyy	__/__/____ dd mmm yyyy	
Name: _____ DoB: __/__/____ Hospital No: _____ Date randomised: __/__/____ TREC trial no: _____	__/__/____ dd mmm yyyy	MRI: Yes <input type="checkbox"/> No <input type="checkbox"/> CT: Yes <input type="checkbox"/> No <input type="checkbox"/> Flexi sigmoid: Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/> Date: __/__/____ dd mmm yyyy Site: _____	Yes <input type="checkbox"/> No <input type="checkbox"/> Date of death: __/__/____ dd mmm yyyy	__/__/____ dd mmm yyyy	

Thank you for your help.

Name of person completing form..... **Date form completed:**/...../.....
dd mmm yyyy

Signature..... **E-mail**.....:..... **Tel no.**.....