ROLARR

RObotic versus LAparoscopic Resection for Rectal cancer

An international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus laparoscopic surgery for the curative treatment of rectal cancer

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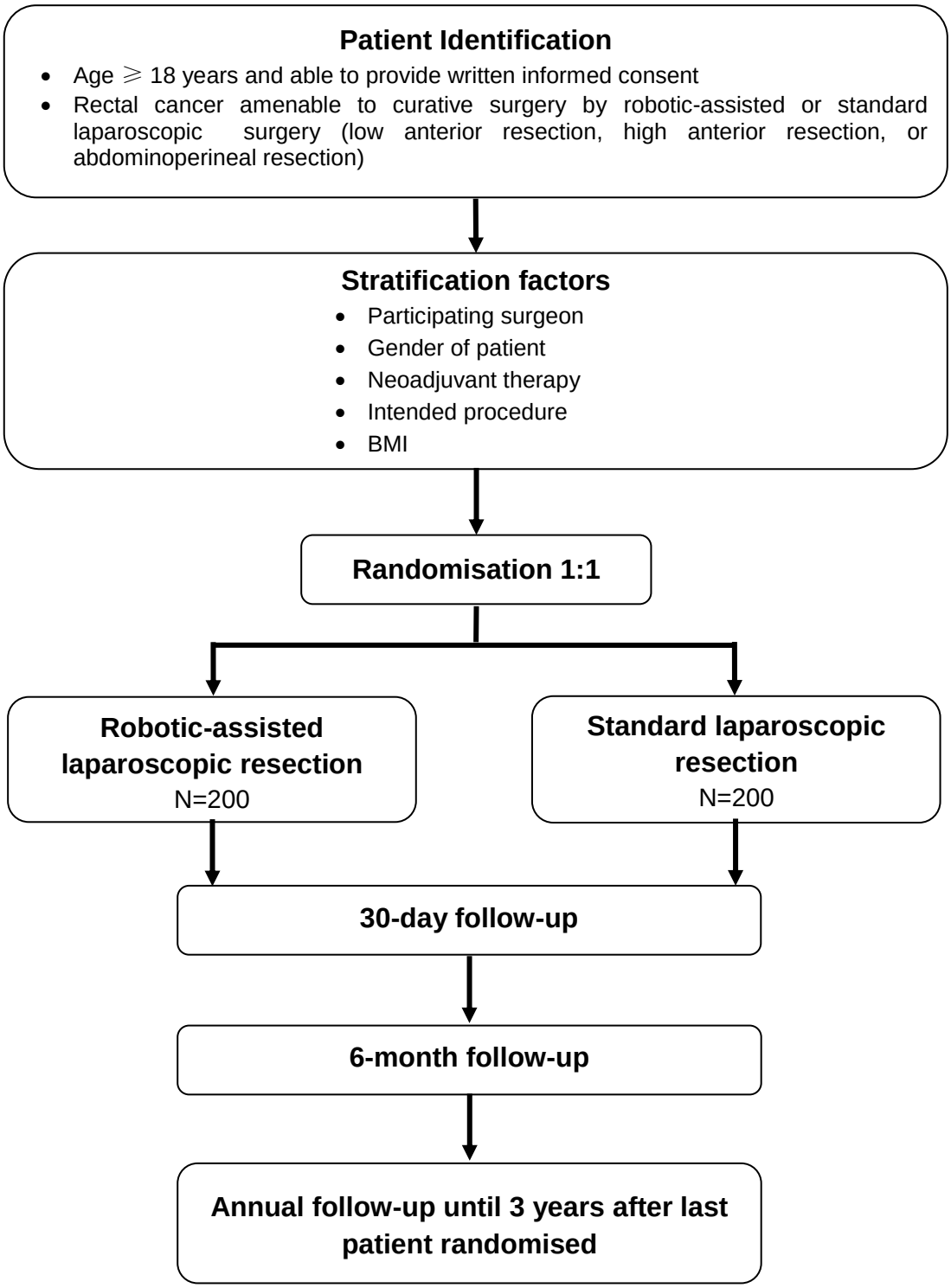
1 Trial Summary



2 Background

2.1 Existing research

The feasibility and safety of laparoscopic surgery has been established for colon cancer[1-3]. The case for rectal cancer is less clear, and of the reported multicentre trials only the MRC CLASICC trial included an evaluation of laparoscopic compared to open rectal cancer surgery[4]. Although both laparoscopic and open rectal cancer resection were associated with similar lymph node yields, concern was expressed at the higher rate of circumferential resection margin (CRM) involvement in the laparoscopic arm (12.4%) as compared to the open arm (6.3%) for patients undergoing anterior resection. This however did not translate into a difference in local recurrence at either 3-year[1] or 5-year follow-up[5]. The difference in CRM involvement was felt to reflect the increased technical difficulties associated with the laparoscopic technique in the rectal cancer subgroup. This was supported by the higher conversion rate in the laparoscopic rectal subgroup (34%) as compared to the laparoscopic colon subgroup (25%)[4]. Analysis of CLASICC data revealed higher morbidity and mortality rates associated with laparoscopic cases converted to open operation (30-day morbidity: laparoscopic 29%, converted 45%; in-hospital mortality: laparoscopic 1%, converted 9%). Some of this increased morbidity may be related to more advanced cancers requiring conversion, but a proportion will inevitably have resulted from the increased operative time, increased technical difficulty, and the need for a laparotomy wound in converted cases.

The introduction of robotic-assisted laparoscopic surgery using the da Vinci™ system (Intuitive Surgical, California, USA) promises to eliminate many of the technical difficulties inherent in laparoscopic surgery[6, 7]. It offers the advantages of intuitive manipulation of laparoscopic instruments with 7-degrees of freedom of movement, a 3-dimensional field of view, a stable camera platform with zoom magnification, dexterity enhancement, and an ergonomic operating environment. Experience has shown that the benefits of the robot are most appreciated when surgical accuracy is required within a confined space, such as the pelvis.

Laparoscopic rectal cancer surgery is technically demanding requiring accurate pelvic dissection according to total mesorectal excision (TME) principles with autonomic nerve preservation. Inadvertent injury to the nerves has been attributed to the higher rate of male sexual dysfunction following laparoscopic surgery[8]. The practicalities of robotic-assisted colorectal cancer surgery have been reported in small series[9, 10] but only two studies[11, 12] have concentrated on rectal cancer, and only one of these performed a randomised comparison in a small number of patients[11].

The literature on robotic-assisted colon surgery is limited to 17 small case series. Most of these comprise mixed benign and malignant disease. The largest by D'Annibale et al reported 53 robotic-assisted colectomies and compared outcomes with 53 laparoscopic resections[13]. It concluded that robotic-assisted surgery was as safe and effective as laparoscopic, was particularly useful in pelvic dissection, but that cost-effectiveness needed further evaluation. Other reports concur that robotic-assisted colorectal surgery is feasible and safe, with low rates of conversion, morbidity and mortality, but with increased operative times[14]. There is only one study which has addressed the issue of hospital costs. This compared 30 robotic-assisted with 27 standard laparoscopic cases and concluded that the total hospital cost was higher for robotic surgery[15].

The feasibility of robotics for TME rectal cancer resection was established by Pigazzi et al in a series of 6 low rectal cancers[12]. A subsequent follow-up study of 39 rectal cancers treated prospectively by robotic-assisted resection reported a zero rate of conversion with a mortality of 0% and morbidity of 12.8%[16]. The only randomised trial compared 18 patients assigned to robotic-assisted resection with 18 patients assigned to standard laparoscopic

resection[11]. No difference was observed in the operative times, the conversion rates (2 laparoscopic, 0 robotic), or the quality of mesorectal resection. The only difference was the length of hospital stay, which was significantly shorter following robotic-assisted laparoscopic surgery (robotic-assisted: 6.9 +/-1.3 days; standard laparoscopic: 8.7 +/-1.3 days, p<0.001) and attributed to a reduction in surgical trauma by the authors. In addition to original reports, there has been one systematic review of robotic-assisted colorectal surgery, which concluded that “robotic colorectal surgery is a promising field and may provide a powerful additional tool for optimal management of more challenging pathology, including rectal cancer”[17].

The current proposal aims to test the hypothesis that robotic-assistance facilitates laparoscopic rectal cancer surgery. On short-term follow-up this should result in a reduction in the conversion rate and no worsening of the CRM positivity rate. On longer-term follow-up, the increased accuracy should improve post-operative bladder and sexual function, enhance quality of life (QoL), and ensure there is no increase in local disease recurrence.

There is a growing enthusiasm for robotics in many surgical specialities. This enthusiasm is often not supported by data on clinical or cost-effectiveness derived from rigorous evaluation by randomised controlled trials. This is the case for robotic-assisted rectal cancer surgery. Given the expense associated with the robotic systems and the limited evidence to support clinical and economic benefits, it is essential that a proper assessment of this new technology is performed in timely manner before its widespread recommendation or implementation. A randomised trial of robotic-assisted versus standard laparoscopic rectal cancer surgery is now urgently needed.

2.2 Risks and benefits

Robotic-assisted laparoscopic rectal cancer surgery is currently being performed in several centres throughout the world. It is from this pool of active robotic centres that the participating ROLARR investigators are drawn. All participants have an established track record and international reputation in laparoscopic and robotic rectal cancer resection.

It is possible that patients would have undergone robotic-assisted surgery irrespective of their inclusion in this trial. The alternative is that patients would have undergone a standard laparoscopic rectal resection, which is the comparator arm of the trial. It is unlikely that any of the proposed patients would have undergone traditional open surgery, as this is no longer the preferred treatment option in any of the participating sites. The exception is the patient with a locally advanced cancer not amenable to curative surgery or a locally advanced cancer requiring multi-visceral excision; these patients are probably still best treated by open surgery and are excluded from this trial.

There are therefore no additional risks to patients participating in this trial, above that normally associated with routine clinical practice. The clinical indications and contra-indications for robotic-assisted surgery are exactly the same as those for standard laparoscopic surgery; in essence robotic-assisted surgery is a laparoscopic operation performed with the help of a robotic-system. However, there is a theoretical risk that patients randomised to a robotic-assisted procedure would be subjected to the risk of technical malfunction of the robotic-system, as compared to those randomised to standard laparoscopic resection. No incidence of this has ever been reported in the literature or made known to the applicants by personal communication. The risk is therefore perceived to be minimal and no greater than might ordinarily have been expected had the patient undergone robotic surgery as part of routine clinical practice. It is anticipated that this risk will be managed by individual participating institutions as part of their normal procedures for governance and covered by normal indemnity arrangements.

Those patients randomised to robotic-assisted laparoscopic surgery may gain from the potential benefits derived from enhanced rectal resection with the use of the robotic system.

These might include a lower rate of conversion to open operation with reduction in post-operative morbidity, increased accuracy of rectal resection with lower rates of CRM positivity, better preservation of the autonomic pelvic nerves, and improvement in QoL measures.

2.3 Rationale for current study

The safety and efficacy of robotic-assisted laparoscopic surgery have been established for certain operations, most notably radical prostatectomy. Pelvic surgery, including rectal cancer surgery, lends itself to robotic-assistance. However, the experience with robotic-assisted rectal cancer surgery is limited to a few small personal series and one randomised clinical trial. Although this data suggests it is feasible, it has not established a benefit over standard laparoscopic surgery in terms of technical, functional or oncological outcomes. The primary aim of any curative cancer surgery is complete oncological resection of the tumour with minimal morbidity. It is therefore of utmost importance that prior to the widespread use of robotics in rectal cancer surgery, it is subjected to rigorous evaluation. The use of this new technology incurs additional financial burdens on already overstretched health care resources and it is therefore essential to assess the health economics and cost-effectiveness in comparison to alternative treatments. As this trial is unlikely to be repeated, 3-year outcomes and cost effectiveness will be included within this trial. Specifically, it is aimed to provide information on the ability of the robotic system to facilitate laparoscopic rectal cancer resection, its impact on oncological outcomes (short-term and long-term), its effect on functional outcomes and QoL, and its cost-effectiveness in terms of future healthcare decision-making. Currently, and for the foreseeable future, there is only one surgical robotic system, the da Vinci™ robot. To avoid any criticism of commercial bias, it is imperative that an evaluation of this robotic technology is performed independently of the manufacturer.

2.3.1 Justification for a randomised controlled trial

Since this is a new technology, it is essential that a proper evaluation is performed and disseminated prior to its widespread implementation. A timely assessment is imperative and for this reason there is no plan to perform a prior pilot study, which would inevitably delay evaluation by proper scientific methods. The feasibility of robotic-assisted rectal cancer surgery has already been established and preliminary data upon which to base sample size calculations are available. The time is right for a formal randomised controlled trial to provide a definitive answer to the proposed research question.

2.4 Aims and Objectives

The purpose of the trial is to perform a rigorous evaluation of robotic-assisted rectal cancer surgery by means of a randomised, controlled trial. The chosen comparator is standard laparoscopic rectal cancer resection, which is essentially the same procedure but without the use of the robotic device. The two operative interventions will be evaluated for short- and longer-term outcomes. The key short-term outcomes will include assessment of technical ease of the operation, as determined by the clinical indicator of low conversion rate to open operation, and clear pathological resection margins as an indicator of surgical accuracy and improved oncological outcome. In addition, QoL assessment and analysis of cost-effectiveness will be performed to aid evidence-based knowledge to inform NHS and other service providers and decision-makers. These short-term outcomes will be analysed after the last randomised patient has had 6 months of follow-up to provide a timely assessment of the new technology, and made available to the public, clinicians and healthcare providers to inform health-care decision making. Longer-term outcomes will concentrate on oncological aspects of the disease and its surgical treatment with analysis of disease-free and overall survival and local recurrence rates at 3-year follow-up.

3 Design

The trial is an international, multicentre, prospective, randomised controlled, unblinded, parallel-group superiority trial of robotic-assisted versus standard laparoscopic surgery for the curative treatment of rectal cancer. Four-hundred patients will be randomised on an equal basis to either robotic-assisted or standard laparoscopic rectal cancer surgery. The follow-up period finishes 3 years after the final patient is randomised.

3.1.1 Justification for unblinded design

As the two surgical procedures create incisions which can allow the patient to be blinded to the operative procedure performed, it would be preferable scientifically to blind patients to their surgical procedure, particularly in respect of patient-reported outcomes. However, it is anticipated that in practice maintaining the blind would be extremely problematic (e.g. in countries such as the USA where private healthcare insurance companies require disclosure of surgery details). Furthermore, patients will also be seen by many healthcare professionals throughout their time in the trial, increasing the risk that the blind may be broken. As a consequence, the trial design will *not* involve blinding patients to the operative procedure.

It should be noted that the trial endpoints are mainly objective measures and a central blinded assessment of these measures is included where possible (e.g. blinded central assessment of the quality of the plane of surgery).

4 Eligibility

4.1 Patient eligibility

4.1.1 Eligibility of participants should be established prior to commencing neoadjuvant therapy.

4.1.2 Inclusion criteria[1]

1. Aged ≥ 18 years
2. Able to provide written informed consent
3. Diagnosis of rectal cancer[2] amenable to curative surgery[3] either by low anterior resection, high anterior resection, or abdominoperineal resection, for example, staged T1-3, N0-2, M0 by imaging as per local practice; although not mandated, CT imaging with either additional MRI or transrectal ultrasound is recommended to assess distant and local disease.
4. Rectal cancer suitable for resection by either standard or robotic-assisted laparoscopic procedure
5. Fit for robotic-assisted or standard laparoscopic rectal resection
6. American Society of Anesthesiologists (ASA) physical status ≤ 3 (Appendix 2)
7. Capable of completing required questionnaires at time of consent (provided questionnaires are available in a language spoke fluently by the participant)

[1] Please note that patients of any BMI are eligible

[2] For the purposes of the ROLARR trial, rectal cancer is defined as an adenocarcinoma whose distal extent is situated at or within 15cm of the anal margin as assessed by endoscopic examination or radiological contrast study.

[3] Eligibility of participants should be established prior to commencement of neoadjuvant therapy

4.1.3 Exclusion criteria

1. Benign lesions of the rectum
2. Benign or malignant diseases of the anal canal
3. Locally advanced cancers not amenable to curative surgery
4. Locally advanced cancers requiring en bloc multi-visceral resection
5. Synchronous colorectal tumours requiring multi-segment surgical resection (n.b. a benign lesion within the resection field in addition to the main cancer would not exclude a patient)
6. Co-existent inflammatory bowel disease
7. Clinical or radiological evidence of metastatic spread
8. Concurrent or previous diagnosis of invasive cancer within 5 years that could confuse diagnosis (non-melanomatous skin cancer or superficial bladder cancer treated with curative intent are acceptable; for other cases please discuss with Chief Investigator via CTRU)
9. History of psychiatric or addictive disorder or other medical condition that, in the opinion of the investigator, would preclude the patient from meeting the trial requirements
10. Pregnancy[4]
11. Participation in another rectal cancer clinical trial relating to surgical technique

4.1.4 Neo-adjuvant therapy

It is anticipated that many patients will require neo-adjuvant therapy (chemoradiotherapy; long course radiotherapy; short course radiotherapy) prior to surgery. Neo-adjuvant therapy is NOT an exclusion criterion for ROLARR, but details of the neo-adjuvant treatment regimens will be recorded. Eligibility of participants should be established prior to the commencement of neoadjuvant therapy and reassessed on completion of neo-adjuvant therapy.

4.1.5 Concurrent clinical trials

Some patients may be suitable for inclusion in other rectal cancer clinical trials. Patients will not be eligible for entry into other clinical trials of surgical technique. However patients will be suitable for inclusion in ROLARR if they have already participated in a previous non-surgical trial, for example relating to neo-adjuvant therapies. Please contact the Clinical Trials Research Unit (CTRU, University of Leeds) for further clarification.

4.2 Site eligibility

The trial will be performed as an international collaboration, given both the limited number of robotic systems currently in clinical use in the UK and sites with sufficient experience in robotic-assisted rectal cancer resection. Participation of sites will be dependent upon the following criteria:

1. Site able to perform both robotic-assisted and standard laparoscopic rectal cancer surgery
2. Established expertise in clinical trial involvement as determined from sites' feasibility questionnaire
3. Predicted capability to recruit a minimum of 15 patients per year to the ROLARR trial.

[4] It is the local surgeon's responsibility to ensure this is assessed in women of child-bearing potential according to local standard of care.

4.3 Surgeon Eligibility

All participating surgeons must have performed a minimum of 30 minimally invasive (laparoscopic or robotic) rectal cancer resections prior to trial participation; at least 10 of these must be laparoscopic and at least 10 of these must be robotic.

Participating surgeons must also provide the total number of laparoscopic or robotic procedures upon starting the trial, and periodic information on the total number of laparoscopic or robotic procedures they perform during the trial period.

5 Recruitment and Randomisation of Patients

5.1 Recruitment of Patients

A maximum total of 520 patients (a maximum of 260 in each arm) will be recruited into the trial.

5.1.1 Informed Consent

Patients will be approached for possible recruitment following diagnosis and radiological staging, provided they fulfil the inclusion/exclusion criteria (see section 4.1). Patients will be provided with verbal and written details. A verbal explanation of the trial along with the approved Patient Information Sheet (PIS)/Consent Form will be provided by a medically qualified member of the healthcare team for the patient to consider. The PIS will provide detailed information about the rationale, design and personal implications of the trial.

Following information provision, patients should be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. Patients will be given as much time as possible to consider their participation in the trial, ideally they will be allowed 24 hours as a minimum. The right of the patient to refuse consent without giving reasons will be respected.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent for their participation in the trial, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent may only be obtained by the Principal Investigator or another clinically qualified member of the trial team who has received Good Clinical Practice (GCP) training and is approved by the Principal Investigator to take informed consent as documented in the trial Authorised Personnel Log.

The patient consent form with all original signatures must be retained in the Investigator Site File. A copy of the signed consent form should be given to the patient, and a record of the consent process, detailing the date of consent and witnesses, should also be kept in the patient's notes (this may include a copy of the consent form as per local practice). A copy of the signed consent form should also be transferred to the CTRU.

Patients will remain free to withdraw from the trial at any time by revoking consent without giving reasons and without prejudicing any further treatment.

5.1.2 Timing of consent

Written informed consent should be obtained as close to randomisation as possible and must be no more than 28 days before randomisation; it is therefore recommended that written informed consent is obtained following the completion of any neoadjuvant therapy.

5.1.3 Loss of Capacity Following Informed Consent

Loss of mental capacity of a patient after giving informed consent for the trial is expected to be a rare occurrence. Nevertheless, explicit prospective consent will be sought from all patients to allow for the continued collection of safety data and follow-up data via their clinical care team in such an eventuality. In the event of incapacity, patients will not receive any further trial-specific interventions.

5.2 Randomisation

5.2.1 Timing of randomisation

Randomisation should take place as soon as possible after consent is obtained and after patients have completed their baseline patient reported questionnaires (see section 7.10). Randomisation must take place as close to the date of surgery as possible and must be no more than 28 days prior to planned surgery date. However surgeons are strongly encouraged to consent and randomise patients within 14 days of planned surgery date whenever possible. This will be monitored by the Data Monitoring and Ethics Committee (DMEC) (see section 14.1).

5.2.2 Randomisation process

Informed written consent for entry into the trial and baseline patient reported questionnaires must be obtained prior to randomisation (see section 5.1.1). Following confirmation of written informed consent and eligibility, patients will be randomised into the trial by an authorised member of staff at the trial site. Randomisation will be performed centrally using the CTRU automated 24-hour telephone randomisation system. Authorisation codes and personal identification numbers (PINs), provided by the CTRU, will be required to access the randomisation system. The following information will be required at randomisation:

- Patient details, including initials, gender and date of birth
- Name and code (assigned by CTRU) of the research site
- Name of the person making the randomisation
- Name and code (assigned by CTRU) of the treating surgeon
- Confirmation of eligibility
- Confirmation of written informed consent and date obtained
- Stratification factors (see section 5.2.3)
- Planned date of operation

24 hr direct line for randomisation: +44 (0)113 343 9083

5.2.3 Treatment allocation

Patients will be randomised on a 1:1 basis to receive either robotic-assisted or standard laparoscopic rectal cancer surgery and will be allocated a unique trial number. A computer-generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well-balanced for the following patient characteristics, details of which will be required for randomisation:

- Treating surgeon
- Patient gender (male or female)
- Neoadjuvant therapy (yes or no)
- Nature of intended procedure (high anterior resection, low anterior resection or abdominoperineal resection)
- BMI[5] (will be calculated automatically from height (cm) and weight (kg) provided at randomisation) and classified according to WHO criteria:
    - underweight/normal
    - overweight
    - obese class I
    - obese class II
    - obese class III

5.3 Non-randomisation

Participating research sites will be required to complete a log of all patients screened for eligibility who are not randomised either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- Age
- Gender
- Date screened
- Reason not eligible for trial participation, or
- Eligible but declined and reason for this, or
- Other reason for non-randomisation

This information will be requested from sites on a regular basis (at least 3 monthly) by the relevant spoke/hub Clinical Trials Unit (CTU).

6 Intervention Details

6.1 Pre-operative investigation and preparation

Preoperative investigation and preparation will be as per institutional protocol. Although not mandated, it is strongly advised that all patients are fully assessed preoperatively by CT scan and MRI or transrectal ultrasound scan.

[5] According to WHO categorisation (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html accessed 13/11/2013)

6.2 Surgery

Laparoscopic mesorectal resection will be performed in accordance with each surgeon's usual practice. Robotic-assisted laparoscopic surgery may involve either a totally robotic or a hybrid approach; the only absolute requirement being that the robot is used for mesorectal resection. For the purposes of ROLARR, a totally robotic and a hybrid operation are defined as follows:

- A totally robotic operation involves a resection of the entire surgical specimen with the use of robotic-assistance.

- A hybrid operation involves the use of laparoscopic techniques to mobilise the proximal colon with robotic-assistance employed to perform the rectal mesorectal dissection.

In cases of upper rectal cancer it is permissible to perform a partial mesorectal excision with a suitable distal margin, rather than a total mesorectal excision (TME).

The specifics of each operation will be at the discretion of the operating surgeon (e.g. port-site placement, mobilisation of the splenic flexure, inferior mesenteric artery/vein division, high versus low vascular division etc.), as will the decision to convert to an open operation. Details relating to the planned and actual operation will be collected on the baseline and operative case report forms (CRFs).

Conversion to open operation is defined as the use of a laparotomy wound for any part of the mesorectal dissection. The use of a limited laparotomy wound to facilitate a low stapled anastomosis and/or specimen extraction is permissible.

6.3 Post-operative care

Post-operative care will be as per institutional protocol, but patients must be reviewed at 30 days (up to 37 days allowed), and 6 months (± 2 weeks) post-operatively at a minimum. Any further visits will be according to local standard clinical practice.

6.4 Withdrawal of treatment

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the patient themselves. In the event that a patient withdraws prior to randomisation, no further data is required to be submitted. If patients withdraw between randomisation and surgery, collection of follow-up data will still be required but patients will not receive any further trial-specific interventions (including administration of further patient reported questionnaires). For patients withdrawing from the trial after surgery, safety data and follow-up data will continue to be collected but the patient will not receive any further trial-specific interventions (including administration of further patient reported questionnaires).

If a patient explicitly states they do not wish to contribute further data to the trial the CTRU should be informed in writing.

7 Assessment and Data Collection

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File; ISF), which will be provided by the CTRU or Spoke CTU (see section

7.1). Sites will keep copies of all completed CRFs for the trial within the ISF. The CRFs will contain the patient's unique trial number, date of birth, and initials.

7.1 Submission of Trial Data

Given the international nature of the research collaboration a Hub-Spoke-Site model will be employed for data collection. Participating sites will submit data to one of two CTUs:

- Hub CTU: CTRU, University of Leeds, UK
- North American Spoke CTU: University of California, Irvine CTU, California, USA

The CTRU (University of Leeds, UK) will also provide the hub CTU for the trial, electronically receiving all trial data transferred from the other international spoke CTU in California.

Participating sites will record trial patient data on trial-specific paper Case Report Forms (CRFs) and then submit paper CRFs to the appropriate international Spoke CTU for data entry and electronic transfer to the hub CTU (CTRU). Missing and discrepant data will be flagged initially by the relevant Spoke CTU, with additional data validations raised as appropriate from the hub CTU (CTRU) data management team.

7.2 Schedule of Events

The timing of interventions and assessments are summarised in Table 1. All patients will be followed up as per protocol until 3 years after the last patient has been randomised.

Table 1: Schedule of Events

	Screening	Baseline (after informed consent has been obtained and prior to randomisation)	Randomisation	Surgery	Pathology Review	30 d Post-op clinical review[1]	6 m Post-op clinical review[2]	Annual status review[3]
Medical Assessment for eligibility	X					X	X	X
Pre-op investigations for eligibility[4]	X							
Informed Consent	X							
Eligibility CRF		X						
Bladder and sexual function questionnaires (I-PSS and IIEF/FSFI)[5]		X					X	
QoL questionnaire (SF-36v2) [5]		X				X	X	
Fatigue questionnaire (MFI-20)[5]		X				X	X	
EQ-5D[5] (UK/North America only)		X				X	X	
Patient reported questionnaires related to resource utilisation[5] (UK/NA only)						X	X	
Randomisation CRF			X					
Randomisation (24hr automated line)			X[6]					
Surgery				X[6]				
Photograph of specimen[7]					X			
Histopathological exam of specimen[8]					X			
Histopathology CRF					X			
Storage of slides/extra tissue for central review (to be sent in batches)					X[8]			
Operative CRF				X				
30 day review CRF						X		
6 month review CRF							X	
Annual follow-up CRF								X
Non-expediting reporting of complications[9]				X		X	X	
Expedited reporting (<24 h) of unexpected serious complications (USCs)[10]			X (until 30 days post-operation) ◄——►					

[1] First post-operative clinical review for ROLARR must not take place earlier than 30 days, but may take place up to 37 days post-operatively. This does not preclude surgeons from reviewing patients prior to 30 days if this is in line with standard institutional protocols, but such patients must be reviewed again for the purpose of the ROLARR trial between 30 and 37 days post-operatively.

[2] Second post-operative clinical review should take place 6 months ± 2 weeks post-operatively.

[3] Follow-up data will be requested on an annual basis until the last patient has reached 3 years following randomisation. Patient follow-up is not pre-specified in the trial protocol and should be performed as per local clinical practice.

[4] Pre-operative investigations should be as per local practice but it is strongly advised that all patients are fully assessed pre-operatively by CT scan and MRI scan or CT scan and transrectal ultrasound scan as a minimum, although local practice may be followed. It is the local surgeon's responsibility to ensure women of child-bearing potential are assessed for pregnancy according to local standard of care.

[5] EQ-5D© EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group (will be used in the U.K. and North America only). I-PSS© International-Prostate Symptom Score © (I-PSS©) Michael J. Barry, 1992[18]. IIEF International Index of Erectile Function[19] FSFI© - Female Sexual Function Index – developed by Bayer AG, Zonagen, Inc. and Target Health Inc. © 2000. All rights reserved[20]. SF-36v2™ Health Survey © 2000 by QualityMetric Incorporated – All rights reserved. SF-36v2 is a trademark of QualityMetric Incorporated. MFI® Multidimensional Fatigue Inventory (20 item version). ®E. Smets, B. Garssen, B. Bonke[21].

[6] Patient should have their laparoscopic surgery (either robotic-assisted or standard) as close to the time of randomisation as possible, ideally within two weeks. It is however recognised that this will not always be possible and that up to 4 weeks may be required.

[7]Digital photographs of the anterior and posterior of the unopened specimen and sequential cross sectional views of the unopened resection specimen are required. The position of the tumour should be clearly marked on the photograph, e.g. with the use of forceps, and a ruler/tape measure should be visible to enable the size to be recorded (see section 7.5 and Appendix 1).

[8] Resection pathology specimens will be reported using standard methods[23] (fields defined on histopathology CRF). Extra tissue slides/samples will be sent to the central repository should the patient consent to this. Tissue collection is an optional separate study to ROLARR.

[9] Complications may occur at any time. For the purposes of safety reporting for the ROLARR trial, intra-operative complications will be captured on the operative CRF, all other short term complications (occurring ≤ 30 days post-operatively and including any pre-operative complications occurring from randomisation not requiring expedited reporting) will be collected on the 30 day post-operative CRF; longer term complications will be captured on the 6 month post-operative CRF. Complications occurring > 6 months after the operation are expected to be rare and will not be collected for the purpose of the ROLARR trial. Complications occurring from randomisation and within 30 days of the operation which are deemed **unexpected and serious** must be reported within 24 hours using the USC form (see section 8)

[10] See section 8

7.3 Pre-operative Assessments and Data Collection

Pre-operative investigation and preparation will be as per institutional protocol.

Data collected on the randomisation, eligibility and pre-operative CRFs will include:

- Personal details and demographics including height, weight, and gender
- Date of diagnosis[6]
- Pre-operative investigations performed
- Any neo-adjuvant treatment
- Planned operation (high or low anterior resection or abdominoperineal resection)
- Confirmation of eligibility
- Confirmation of written informed consent
- Date of randomisation
- Known concomitant diseases and co-morbidities

Patients will also be asked to complete the baseline generic health-related QoL and fatigue questionnaires (SF-36v2™ and MF®I-20)[21], EQ-5D©, and patient reported bladder and sexual function questionnaires (I-PSS© and IIEF/FSFI©)[18-20] following written informed consent and prior to randomisation.

7.4 Operative Assessments and Data Collection

An operative CRF will be completed. This will collate data relating to the operation including:

- Surgeon
- ASA status
- Laparoscopic technique (robotic-assisted/standard)
- Details of previous abdominal operations
- Type of operation performed (high or low anterior resection or abdominoperineal resection)
- Duration of operation (docking time, robotic time, total operation time)
- Whether outcome of operation curative, palliative or unresectable in the opinion of the surgeon at the time of operation
- Whether robotic-assisted rectal dissection was completed by a standard laparoscopic approach, and reason
- Whether conversion to open surgery occurred, and reason
- Any intra-operative complications

7.5 Pathology Assessment

Histopathological analysis of the rectal resection specimens is recommended according to internationally agreed criteria[22]. Further details are provided in Appendix 1.

A histopathology CRF will be completed including:

- Gross description including site (including above, at or below peritoneal resection margins), maximum tumour size, position of tumour (marked on diagram), distance from distal and proximal resection margins, evidence and site of perforation, plane of

[6] The date of diagnosis is defined as the date of pathological confirmation.

surgical excision (mesorectal, intramesorectal or muscularis propria for mesorectum and extralevator, sphincteric or intrasphincteris/submucosal/perforation for APR only) and distance from dentate line (for APR)

- Histology including type and differentiation, local invasion (including depth of extramural invasion), margin involvement including doughnuts, proximal and distal cut ends, and distance to the non-peritonealised 'circumferential' resection margin (CRM) and whether complete (R0) resection
    - If CRM involved then maximal length of involved margin, mode of involvement at CRM
- Any evidence of response to neoadjuvant therapy (if appropriate)
- Metastatic spread including lymph nodes (number retrieved and number involved, whether apical node involved), lymphatic or extramural vascular invasion, neural invasion, presence of extra-nodal deposits and histologically proven distant metastases
- Co-existent conditions including ulcerative colitis or Crohn's disease
- TNM (v.5) and Dukes' stage[23, 24]

Digital photographs of the anterior and posterior of the specimen and sequential cross sectional views of the surgical specimen, as well as close ups of the front and back of the levator/anal sphincter (if appropriate) will also be collected (prior to dissection). This is to allow blinded assessment of the quality of the plane of surgery. The site of the tumour should be clearly marked (e.g. with forceps) and the photograph should include a ruler/tape measure to enable sizing of the specimen.

As a quality assurance measure, sites will be required to submit copies of all histopathology reports (if reported in English) to the hub CTU (CTRU, UK). **All personal identifiable information must be obliterated from reports prior to sending to the hub CTU.** However, the following patient information should be clearly marked on all local histopathology reports to enable tracking and processing:

- Unique trial number (with site number obscured)
- Initials
- Date of birth
- Local histopathology report number

7.5.1 Central Pathology Slide Review

To enable central pathological review either the original slides or a duplicate set of slides should be submitted. If requested, all slides received will be returned to the originating site after being digitally scanned in Leeds. If return of slides is not requested, slides will be destroyed once the central review for ROLARR is complete. If a high quality digital slide image can be provided by sites then this is an acceptable alternative to submitting slides.

Digital photographs of all slides will be fully anonymised and posted on the LICAP Pathology website, which will be available to all collaborators.

7.5.2 Optional Tissue Block Donation

If locally acceptable, ROLARR trial participants will be invited to donate an additional block of tumour and normal tissue to the Leeds Institute of Cancer and Pathology (LICAP) colorectal tissue bank. Donation of these blocks is not a requirement of the ROLARR trial,

however the CTRU is assisting the LICAP colorectal tissue bank in the collection of appropriate tissue specimens for planned microarray analysis and to support potential future research. These banked tissue blocks will be available for collaborative research for use in ethically approved studies.

ROLARR participants will be asked for consent to obtain their tissue blocks samples under an optional item on the ROLARR consent form. Where consent is given, research staff from the CTRU will request transfer of the fixed tumour block and one normal tissue block from the relevant pathologist. Blocks will be transferred direct to LICAP. In order to maintain confidentiality, **blocks must be labelled only with the patient's unique ROLARR trial number and the ROLARR site code** allocated by CTRU (hence, blocks will be linked anonymised). On receipt at LICAP, blocks will be securely stored in a Human Tissue Authority (HTA, UK) compliant facility.

7.6 Post-operative Assessment and Data Collection

Post-operative care will be as per institutional protocol. However, a 30 day (up to 37 days allowed) post-operative clinical assessment must be carried out for all patients.

Data collected will include:

- Duration of post-operative hospital stay (date fit for discharge, actual discharge date, reason for any delay)
- Post-operative complications and severity
- Details of any further surgery required and reason
- Patient status (alive or dead)

Patients will also complete appropriate questionnaires (SF-36v2™, MFI®-20, EQ-5D© and patient reported questionnaires relating to resource utilisation).

7.7 Follow-up Assessment and Data Collection

A 6 month (± 2 weeks) post-operative clinical assessment must be carried out for all patients. Follow-up data will be collected 6 months post-operatively, and then on an annual basis until the last patient has reached 3 years after randomisation (note that for patients recruited at the start of the study this will mean they are followed up for more than 3 years).

Data collected will include:

- Patient status (alive or dead)
- Details of any adjuvant therapy (only collected on 6 month post-operative CRF)
- Details of any local or distant recurrence, including:
    - Date of recurrence
    - Site of recurrence
    - Method of diagnosis[7]
- Details of any new primary cancer diagnoses
- Details of whether stoma present, or whether reversed since last follow-up

[7] Disease recurrence (local or distance) may be initially detected by radiological follow-up, but should be confirmed by tissue biopsy where possible.

At the 6 month post-operative visit only, data relating to complications will also be collected and patients will also complete appropriate questionnaires (SF-36v2™, MFI®-20, EQ-5D©, patient reported questionnaires related to resource utilisation, I-PSS© and IIEF/FSFI©).

7.8 Death

All deaths must be recorded on the Notification of Death CRF. Data collected will include:

- Date of death
- Cause of death

If a patient dies within 6 months of their operation, a completed Notification of Death CRF should be submitted **within 7 days** of site becoming aware of the event. If a patient dies more than 6 months after their operation then a completed Notification of Death CRF will be collected with annual follow-up data (see section 8.4).

7.9 Pregnancy

Any suspected or confirmed pregnancies between the date of randomisation to the date of surgery must be reported to the CTRU **within 7 days** of the site becoming aware. All protocol treatment must be stopped immediately if a pregnancy occurs or is suspected during this time; it is the responsibility of the treating surgeon to decide what course of action should be taken in relation to ensuring the participant's ongoing treatment outside of the trial protocol.

The CTRU will inform the Sponsor of all reported pregnancies.

7.10 Quality of Life and Health Economic Assessment

The EQ-5D©, generic health-related quality of life (SF-36v2™) and fatigue (MFI®-20) data will be collected at baseline and at 30 days and 6 months post-operative visits (see section 9). Patient reported medical resource utilisation will be measured at 30 day and 6 month post-operative visits. In addition patient reported bladder and sexual function questionnaires (I-PSS©, IIEF/FSFI©) will be completed at baseline and at the 6 months post operative visit.

EQ-5D© and the patient-reported medical resource utilisation questionnaire will only be required to be completed in patients recruited from the UK and North America (see Section 10).

7.11 Definition of End of Study

The end of the study is defined as 3 years after the date that the last patient has been randomised to the trial.

8 Safety Reporting

For the purpose of the ROLARR trial the safety reporting terms adverse events and serious adverse events have been translated into complications.

8.1 General Definitions

A complication is defined as an untoward medical event in a patient, which has a causal relationship to the trial. The trial includes the surgical intervention and any trial specific interventions e.g. the consent process and completion of questionnaires.

An untoward medical occurrence can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease (other than rectal cancer)
- any clinically relevant deterioration in any laboratory assessments or clinical tests

A **serious** complication is defined as a complication which:

- results in death
- is life-threatening[8]
- requires in-patient 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

A **serious** complication which is **related** and **unexpected** (termed **Unexpected Serious Complication**, or **USC**) will require expedited reporting (see section 8.3.1) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The National Research Ethics Service (NRES; UK) defines the terms **related** and **unexpected** as:

- **Related**: that is, it resulted from administration of any research procedures. All complications by definition are related to the trial procedures. (Untoward medical events which are unrelated to the trial procedures are not being collected in this trial.)
- **Unexpected**: that is, the type of event that in the opinion of the investigator is not considered expected. Examples of expected complications are provided in section 8.2; note this is not an exhaustive list.

Rectal cancer progression, new primary cancers, and death due to disease progression will be collected separately as secondary endpoints. Untoward medical events that are associated with rectal cancer progression, new primary cancers, and death due to progression should not therefore be reported as complications.

[8] Life-threatening refers to an event in which the patient was at risk of death at the time of the event, NOT an event which hypothetically may have caused death had it been more severe.

8.2 ROLARR Expected Complications

Operative

- Damage to organ/structure e.g.
  - Bowel
  - Bladder/ureter
  - Major vessel
  - Nerves
- Faecal contamination
- Haemorrhage
- Surgical emphysema
- Failure of surgical equipment laparoscopic equipment or robotic system including hardware/software malfunction

Post-operative Complications

- Gastrointestinal
  - Anastomotic leak
  - Gastrointestinal fistula
  - Gastrointestinal ischaemia/necrosis
  - Gastrointestinal obstruction
  - Gastrointestinal perforation
  - Gastrointestinal stricture/stenosis
  - Gastrointestinal ulceration
  - Protracted Ileus (>3 days)
- GI Infection
  - Intra-abdominal/pelvic abscess
  - Post-operative peritonitis
  - Pseudomembranous colitis
- Stoma
  - Stoma prolapse/retraction
  - Stoma dehiscence
  - Stoma necrosis
  - Overactive stoma (>1.5 L per 24 hours for >1 week)
- Renal / Urinary
  - Acute renal failure
  - Urinary retention
  - Urinary tract infection
- Vascular
  - Cerebrovascular accident/stroke
  - Distal limb ischaemia/compartment syndrome
  - Deep vein thrombosis (DVT)
- Wound
  - Wound infection
  - Wound dehiscence
  - Incisional hernia
- Miscellaneous
  - Back pain
  - Cholecystitis
  - Delirium
  - Haemorrhage
  - Pancreatitis
  - Pressure sore
  - Subcutaneous emphysema

Cardiorespiratory Complications
(May be operative or post-operative)

- Respiratory, including
  - Respiratory failure
  - Aspiration
  - Pleural effusion
  - Pneumonia/chest infection
  - Pulmonary embolus
- Cardiac, including
  - Arrhythmia
  - Cardiac failure
  - Ischaemic heart disease/ myocardial infarction
- Cardio-respiratory arrest

8.3 Reporting of Complications

Information on all complications will be collected for this trial whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation.

8.3.1 Unexpected Serious Complications (USCs) occurring within 30 days of surgery – Expedited reporting

All USCs (see section 8.1) occurring from randomisation and up to 30 days following completion of rectal cancer resection are subject to expedited reporting requirements and must therefore be notified to the CTRU **within 24 hours** of the clinical research staff becoming aware of the event. Notifications should be sent to CTRU by fax using the USC Case Report Form (CRF).

24 hr fax for reporting USCs: +44 (0)113 343 6774

For each USC, the following data will be collected:

- Start and end dates of event, if resolved Full details of complication in medical terms with a diagnosis (if possible)
- Action/intervention
- Outcome
- An identifiable and authorised reporting source (i.e. the signature of the investigator or other medic authorised by the investigator at the reporting site)

Any follow-up information on USCs should be faxed to the CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. All USCs will be reviewed by the Chief Investigator and subject to expedited reporting to the Sponsor and the main REC by the CTRU on behalf of the Chief Investigator in accordance with current NRES guidance, CTRU SOPs, and Sponsor requirements.

USCs with an onset date greater than 30 days post-surgery are not subject to expedited reporting, but should be reported with all other types of complication (i.e. all expected complications and non-serious unexpected complications) via a post-operative complication form submitted with the 30 day or 6 months post-operative CRFs, as appropriate (see section 8.3.2).

8.3.2 All other complications – Non-expedited reporting

Information about the incidence and severity of all other complications (this includes all expected complications and non-serious unexpected complications) which occur from the date of operation until 6 months post-operatively will be collected for all patients via a post-operative form submitted with the operative CRF, 30 day post-operative CRF or 6 month post-operative CRF, as appropriate. This also applies to any unexpected serious complications with an onset date greater than 30 days post surgery.

These events will **not** be subject to expedited reporting requirements.

Complications occurring > 6 months post-operatively (this includes USCs) will not specifically be collected for the purposes of the ROLARR trial.

8.3.3 Untoward medical events unrelated to the trial – Not reportable

It is anticipated that there will be minimal additional risks associated with the interventions in this trial. Patients treated may have co-morbidities other than their rectal cancer and in recognition of this, untoward medical events will only be reported if they are classified as related to trial procedures (including the surgical intervention and related procedures or trial specific procedures such as consent and questionnaire completion).

8.4 Deaths

Deaths occurring in the trial population from the date of randomisation to 3 years after the last patient has been randomised must be reported on the Notification of Death CRF. If they occur within 6 months of the patient's operation then this form must be faxed to the relevant Spoke/Hub CTU within 7 days of the research staff becoming aware of the event. The original form should then be posted to the Spoke/Hub CTU and a copy retained at the site. Deaths occurring more than 6 months after the operation must also be reported on the Notification of Death CRF but this can be done at the time of annual follow-up and returned with the annual follow-up CRF to the Spoke/Hub CTU.

8.5 Serious Breaches of Good Clinical Practice (GCP)

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach that they become aware of. A serious breach of the protocol is classed as a serious breach which is made without permission as a result of error or fraud/misconduct. Minor protocol deviations are agreed with the Sponsor or CI either in advance or as soon as possible after the event.

In the event of any doubt, or for further guidance, the Investigator should contact the CTRU.

8.6 Responsibilities for Safety Reporting

Principal Investigator (i.e. Lead trial clinician at each recruiting site or appropriate clinical individual identified in trial delegation log)

- Checking for complications during admission and follow-up, including judgment in assigning:
    - causality i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
    - seriousness
    - expectedness
- To ensure all USCs up to 30 days post-operation are recorded and initially reported to the CTRU (hub) within 24 hours of the research team becoming aware and to provide further follow-up information as soon as available.
- To report USCs to local coordinating spoke CTU and local committees in line with locally agreed arrangements.

Chief Investigator (or nominated individual in CI's absence)

- Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment.
- Undertake review of Unexpected Serious Complications (USCs) (see section 8.1).
    - In the event of disagreement between local assessment and the Chief Investigator, local assessment may be upgraded or downgraded by the Chief Investigator prior to reporting to the main REC.

CTRU (Hub CTU)

- Expedited reporting of USCs to the main REC and Sponsor within required timelines.

- Preparing annual safety reports to the main REC and periodic safety reports to the TSC and DMEC as appropriate.
- Notifying Investigators of USCs which compromise patient safety.

North American Spoke CTU

- Ensure adherence to local (country-specific) safety reporting arrangements
- Ensure sites are aware of and comply with processes for reporting USCs direct to the CTRU hub within stipulated timeframes.

Trial Steering Committee (TSC)

- Periodic review of safety data in accordance with the TSC Terms of Reference, and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

- In accordance with the DMEC Terms of Reference, periodic review of unblinded safety data to determine patterns and trends of events and to identify any safety issues which would not be apparent on an individual case basis.

8.7 Reporting

UK safety issues will be reported to the main UK REC in the annual progress report.

An annual summary of all events will be reported to the TSC and sponsor.

Expedited reporting of events (as detailed in section 8.3.1) to the main REC and sponsor will be subject to current NRES guidance, CTRU SOPs and sponsor requirements.

9 Quality of Life

Patients' quality of life (QoL), fatigue and bladder and sexual function will be assessed by patients' self-reported symptoms and patients' self-reported utilities. It is of particular importance to assess bladder and sexual function as dysfunction in these areas is a recognised complication of laparoscopic rectal resection. This is due to inadvertent damage to the pelvic hypogastric and splanchnic nerves[8].

To assess bladder function, the International Prostatic Symptom Score (I-PSS©)[18] will be used. This questionnaire includes seven questions relating to lower urinary tract function, which form an overall symptom score that can be used to classify bladder dysfunction as mild, moderate or severe[18]. To assess sexual function, the International Index of Erectile Function (IIEF)[19] and Female Sexual Function Index (FSFI©)[20] will be used. Both are brief male/female-specific questionnaires developed to assess various domains of sexual function. All 3 questionnaires obtain information relating to patient's functioning over the previous 4 weeks. The I-PSS©, IIEF and FSFI© were all used to assess patient-reported bladder and sexual functioning in a postal survey of patients recruited to the MRC CLASICC trial[8].

In addition, the SF-36v2™, a well validated, multi-purpose standard health-related QoL evaluation questionnaire, will be used to assess generic QoL. It generates an 8-scale profile of functional health and well-being scores, as well as summary measures of physical and mental health. This information again relates to the previous 4 week time period. In addition, the EQ-5D© questionnaire will be used to assess self-reported utility. This is a standardised

non-disease specific instrument which describes and values health-related QoL and provides a single index value for a number of different health states. The EQ-5D© will only be assessed in patients recruited from UK and American sites.

To assess fatigue, the Multidimensional Fatigue Inventory (MFI®-20) will be used[21]. The MFI® is a 20-item self-report validated instrument designed to measure current fatigue. It creates a global score as well as individual scale scores that cover the following dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue.

Patients will be asked to complete all questionnaires prior to randomisation (baseline) and at 6 months post-operatively. **Baseline questionnaires should be given to patients in clinic immediately after consent has been obtained and must be completed prior to randomisation** (randomisation should take place immediately following completion of baseline questionnaires). Patients will be asked to also complete the SF-36v2™, MFI®-20 and EQ-5D© questionnaires at the 30 days post-operative visit, in addition to the above time points.

Questionnaires will be completed by patients at the time of clinical assessment, but before any medical assessments or blood tests are performed. Patients will be asked to seal the questionnaires in envelopes prior to being given to research staff. Research staff will then send the sealed envelopes to the Spoke/Hub CTUs for entry into the database.

10 Economic Evaluation

The use of this new technology will change the distribution and quite possibly the magnitude of health care resource utilisation for this indication, in the context of an already stretched health care budget. It is therefore essential to assess its cost-effectiveness in comparison to alternative treatments. Currently, and for the foreseeable future, there is only one surgical robotic system, the da Vinci™ system. To avoid any criticism of commercial bias, it is necessary that an evaluation of this robotic technology is performed independently of the manufacturer.

An economic evaluation will be performed using a UK NHS perspective to aid the development of an evidence-base to support NHS service providers and budget holders in their decision making processes. The evaluation will first estimate the expected incremental cost effectiveness of robotic resection compared to laparoscopic resection at 6 months. This will be extrapolated using a decision analytic model to estimate lifetime cost-effectiveness, with 3 year clinical follow-up data being used to reduce uncertainty about the long term impact of robotic versus laparoscopic surgery. In order to do this, the trial will collect information on the ability of the robotic system to facilitate laparoscopic rectal cancer resection, its impact on oncological outcomes (short-term and long-term), and its impact on functional outcomes and QoL.

The outcome measure for the economic evaluation will be Quality Adjusted Life Year (QALY), where QoL will be measured using the EQ-5D© and valued using the standard UK tariff[2625]. EQ-5D© data will be obtained using English-language version questionnaires from patients recruited from UK and North American trial sites. The data will be collected at baseline, 30 days and 6-months post-operatively. Multiple imputation methods will be used to estimate QoL for those patients not completing this questionnaire. In this way, the analysis will include QoL for all patients in the trial, regardless of language.

Costs will be estimated using UK NHS unit costs from national data sources such as the NHS Reference Costs database and the Personal Social Services Research Unit (PSSRU) costs of health and social care. Clinical outcomes will be extracted from the trial CRFs for all patients in the trial and used within the economic analysis. An NHS resource usage will be

identified for each CRF in consultation with the UK clinicians involved in the trial. This is likely to focus upon costs incurred by hospital-based services.

A separate patient-completed resource usage questionnaire will also be used that focuses on community-based medical resource usage (e.g. GPs, nurses, physiotherapists/occupational therapists, outpatients, and medications). This questionnaire will be used at 30 days and 6 months in UK and North American sites. (It is assumed that clinical practice in the UK and North America is comparable but the analysis will also consider scenarios in which only UK data is used.) Where possible, community resource usage will be attached to CRF clinical outcomes; where not, they will be attached to the relevant trial arm. In this way, potential NHS costs can be inferred for all patients in the trial, regardless of site. (In addition to these costs, we must also apportion a fraction of the cost of the robotic device to the robotic arm of the trial. The methods used to do this are under development and are separate from this protocol.)

Once costs and QALYs are identified for each patient we will estimate the incremental cost-effectiveness of robotic versus laparoscopic surgery. In long term models, costs and outcomes will be discounted at 3.5% in line with NICE recommendations.

Given the need to impute outcomes for a significant proportion of patients recruited to the trial, the analysis of uncertainty will be an important part of the economic evaluation. Probabilistic sensitivity analysis of parameter uncertainty will be undertaken using non-parametric bootstrap techniques and presented using standard techniques (Expected Net Benefit, Cost Effectiveness Acceptability Frontiers). Global value of information will also be reported and a partial value of information estimates calculated for selected parameters to inform subsequent research.

A comparison of operative times between the two techniques will also be considered in addition to other health-care economic outcomes, and will be summarised as part of the analysis of operative and short-term outcomes.

11 Endpoints

11.1 Primary Endpoint

The primary endpoint is the rate of conversion to open surgery as an indicator of surgical technical difficulty. Conversion is defined as the use of a laparotomy wound for any part of the mesorectal dissection. The use of a limited laparotomy wound to facilitate a low stapled anastomosis and/or specimen extraction is permissible and not defined as an open conversion.

11.2 Secondary Endpoints

Two key secondary endpoints, which reflect accuracy of surgery (oncological efficacy), are as follows:

- Pathological CRM positivity rates as recorded from local histopathology review, where resection margin positivity is defined as a distance of ≤1mm of the cancer from any resection margin.
- 3-year local recurrence rates as calculated from the cumulative incidence function plot of time to local recurrence, where time to local recurrence is defined as the time

from date of randomisation to date of local recurrence[9]. Local recurrence is defined as evidence of locoregional disease within the surgical field.

Further secondary endpoints include the following:

- Intra-operative and post-operative (30 day and 6 month) complications and 30-day operative mortality. Thirty-day operative mortality is defined as deaths occurring from any cause during the first 30 post-operative days.
- Patient self-reported bladder and sexual function as assessed by the I-PSS© for male and female bladder function, and the IIEF and FSFI© for sexual function.
- Patient self-reported generic health related QoL as assessed by the SF-36v2™ and fatigue assessed by the MFI®-20.
- Three-year disease-free and overall survival. Overall survival is defined as the time from date of randomisation to date of death from any cause. Disease-free survival is defined according to Punt et al's definitions[26] as the time from date of randomisation to date of death from any cause, recurrent disease (locoregional or distant recurrence) or second primary cancer [7].
- Health economics:
    - Preference based QoL measured by EQ-5D© and used to calculate quality-adjusted life-years (QALYs).
    - Direct resource utilisation
    - Cost-effectiveness estimated using QoL and direct resource use information combined with apportioned cost scenarios of the robotic device.
- Quality of the plane of surgery as assessed by local histopathology review, using the grading criteria given in Appendix 1.

12 Statistical Considerations

12.1 Sample size

The primary endpoint is conversion to open rectal resection; the sample size has therefore been based on ensuring sufficient numbers of patients are recruited to reliably address this endpoint. The conversion rate in the MRC CLASICC trial for rectal cancer resection was 34%[4]; a more realistic and current conversion rate for a group of experienced laparoscopic surgeons would be ~25%[27]. Although the literature regarding rectal robotic-assisted surgery is limited and restricted mostly to single-centre case series experiences of both benign and malignant disease, low rates of conversion (0% to 2.6%) are reported[11, 12, 16]. Information from the ROLARR clinical leads, based on a combined personal experience of >150 cases, has indicated a conversion rate for robotic-assisted rectal cancer surgery of between 5% and 8%. A relative reduction of at least 50% (in absolute terms, 25% to 12.5% in the robotic-assisted laparoscopic arm) is therefore strongly believed to be achievable and also represents an extremely clinically important difference, not only in terms of outcomes for health-care providers but also in terms of patient-related outcomes as it has been shown that patients who convert during surgery have worse outcomes[4, 28]. Therefore using a conversion rate of 25% for standard laparoscopic surgery and a 50% relative reduction to be clinically relevant, with 80% power and a 5% (2-sided) significance level, 336 patients will be required using a two-group continuity corrected chi-squared test of equal proportions (nQuery Advisor® 6.01). A minimum of 400 patients (200 per arm) will therefore be recruited

[9] The date of recurrence/secondary cancer is defined as the date of the relevant (e.g. clinical or radiological) assessment which detects the recurrence/secondary cancer..

to allow for early withdrawals, cross-over, protocol violations (e.g. benign tumours) and missing follow-up data, to provide a minimum of 80% study power.

A maximum of 520 patients (260 per arm) will be recruited. A sample size of 520 patients, under the assumptions outlined above, will provide 90% study power. As we approach the target minimum sample size of 400 patients, remaining recruitment time and funding will be assessed and further patients recruited if feasible, up to a maximum of 520 patients in total.

As mentioned above the sample size is based on the primary endpoint; although it is not a requirement to ensure sufficient power for the secondary outcomes, the minimum sample size of 400 patients will be adequate to obtain meaningful conclusions regarding the key secondary endpoints of CRM positivity rate and 3-year local recurrence rate as follows:

For the CRM positivity endpoint, the rates are expected to be similar in the two arms however to examine equivalence in isolation will require numbers beyond that achievable. A practical approach is to therefore examine the absolute difference between the arms for this endpoint, i.e. focus on the width of the confidence interval (CI) for the difference, rather than on the outcome of a significance test[29], as adopted in the MRC CLASICC trial[4]. The CRM positivity rate in the MRC CLASICC trial was 16% for laparoscopic rectal cancer resection however this may now not reflect the current CRM positivity rate amongst a group of experienced laparoscopic surgeons. Table 2 below shows the likely widths of the 95% CI for various absolute differences in the CRM positivity rates based on a range of rates in the laparoscopic arm and using 400 patients as the total number to be recruited. Regarding CIs of approximately 10% around differences to be clinically significant, the approach and definition taken for the MRC CLASICC trial[4], the results of which have changed practice (NICE technology appraisal guidance 105[30], the table indicates that 400 patients will be sufficient to be able to reliably answer this question.

Table 2: Likely maximum widths of the 95% CI for various absolute differences in the CRM positivity rates (given minimum sample size of 400 patients)

Total number of patients	Laparoscopic surgery	Robotic-assisted surgery	Difference in CRM positivity rate	95% CI for difference
400	16%	15%	1%	(-8.1%, 6.1%)
	16%	14%	2%	(-9.0%, 5.0%)
	16%	11%	5%	(-11.7%, 1.7%)
400	15%	14%	1%	(-7.9%, 5.9%)
	15%	13%	2%	(-8.8%, 4.8%)
	15%	10%	5%	(-11.5%, 1.5%)
400	14%	13%	1%	(-7.7%, 5.7%)
	14%	12%	2%	(-8.6%, 4.6%)
	14%	9%	5%	(-11.2%, 1.2%)
400	13%	12%	1%	(-7.5%, 5.5%)
	13%	11%	2%	(-8.4%, 4.4%)
	13%	8%	5%	(-11.0%, 1.0%)

For the 3-year local recurrence endpoint, as the rates are also expected to be similar in the two arms, but again to examine equivalence in isolation will require numbers beyond that achievable, it is proposed to examine the absolute difference between the arms and focus on the width of the confidence interval as per the CRM positivity endpoint. The 3-year local recurrence rate in the MRC CLASICC trial was 9.7% for laparoscopic rectal cancer

resection[1] however this may now not reflect the current 3-year local recurrence rate amongst a group of experienced laparoscopic surgeons. Table 3 below shows the likely widths of the 95% CI for various absolute differences in the 3-year local recurrence rates based on a range of rates in the laparoscopic arm and using 400 patients as the total number to be recruited. As per the approach taken for the CRM positivity endpoint, regarding confidence intervals of approximately 10% around differences to be clinically significant, the table indicates that 400 patients will be sufficient to be able to reliably answer this question. Although there is no long-term outcome data available for rectal cancer robotic resection to indicate what the treatment effect will be, as the difference in local recurrence rates at 3 years between laparoscopic and open rectal cancer resection in the MRC CLASICC trial was 0.3%[1], if this can be extrapolated as the difference between the extremely similar techniques of robotic assisted and standard laparoscopic surgery, 400 patients will be sufficient to establish confidence intervals of approximately 5% around the difference.

Therefore 400 patients in total will be recruited to this trial from an anticipated minimum of 20 sites. As the number of robots in clinical practice and the necessary expertise is as yet limited in the UK, this necessitates that the trial is conducted as an international collaboration.

Table 3: Likely maximum widths of the 95% CI for various absolute differences in the 3-year local recurrence rates (given minimum sample size of 400 patients)

Total number of patients	Laparoscopic surgery	Robotic-assisted surgery	Difference in 3-yr recurrence rate	95% CI for difference
400	10%	9%	1%	(-4.7%, 6.7%)
	10%	8%	2%	(-3.6%, 7.6%)
	10%	5%	5%	(-0.1%, 10.1%)
400	9%	8%	1%	(-4.5%, 6.5%)
	9%	7%	2%	(-3.3%, 7.3%)
	9%	4%	5%	(0.2%, 9.8%)
400	8%	7%	1%	(-4.2%, 6.2%)
	8%	6%	2%	(-3.0%, 7.0%)
	8%	3%	5%	(0.6%, 9.4%)
400	7%	6%	1%	(-3.8%, 5.8%)
	7%	5%	2%	(-2.7%, 6.7%)
	7%	2%	5%	(1.0%, 9.0%)

13 Statistical Analysis

Statistical analysis is the responsibility of the CTRU Statistician. A full statistical analysis plan will be written before any analyses are undertaken and in accordance with CTRU standard operating procedures.

Analysis will be performed on an intention-to-treat (ITT) basis (primary analysis), where patients will be included according to the surgical procedure they were randomised to, and by actual treatment group, where patients will be included according to the surgery actually

received (laparoscopic, robotic-assisted or converted to open surgery). All hypothesis tests will be two-sided and use a 5% significance level. Where appropriate, analyses will account for the hierarchical structure of the data, allowing for multiple levels of variation of the endpoints - both “within” and “between” operating surgeon.

The difference in the proportion of patients who are converted to open surgery intra-operatively (defined as the use of a laparotomy wound for any part of the mesorectal dissection) between the treatment groups will be compared using logistic regression to adjust for the stratification factors. Odds ratios and corresponding 95% confidence intervals and also confidence intervals of the difference in conversion rates will be presented. Sensitivity analysis will be considered to account for missing data. The proportion of patients who convert from robotic-assisted to laparoscopic surgery intra-operatively will also be summarised.

The differences in the proportion of patients who have a positive circumferential resection margin (defined as a distance of ≤1mm of the cancer from the resection margin as recorded from the local histopathology review) between the treatment groups will be compared using logistic regression to adjust for the stratification factors. Odds ratios and corresponding 95% confidence intervals and also confidence intervals of the differences in pathological CRM positivity rates will be presented. Sensitivity analysis will be considered to account for missing data.

Time to local recurrence is defined as the time from date of randomisation to date of local recurrence; patients with missing follow-up data or who are alive and local recurrence-free at the time of analysis, will be censored at the last date they were known to be alive and local-recurrence free. Patients without evidence of local recurrence at death will be censored at the date of death in the regression analysis. Cumulative incidence functions for time to local recurrence will be calculated and differences between the treatment groups at 3 years compared using Cox’s proportional hazards model, if appropriate, to adjust for the stratification factors. Hazard ratios and corresponding 95% confidence intervals and also confidence intervals of the differences in 3-year local recurrence rates will be presented. Sensitivity analysis will be considered to account for missing data.

The differences in the proportion of patients who have an intra-operative complication (defined as an adverse event occurring during surgery related to the surgical procedure and related procedures e.g. anaesthetic) between the treatment groups will be compared using logistic regression to adjust for the stratification factors. Odds ratios and corresponding 95% confidence intervals and also confidence intervals of the differences in complication rates will be presented. Sensitivity analysis will be considered to account for missing data.

The differences in the proportions of patients who have a 30-day and a 6-month post-operative complication (defined as an adverse event occurring during the first 30 days and 6 months post-operatively respectively and related to surgery and related procedures e.g. anaesthetic) between the treatment groups will be compared using logistic regression to adjust for the stratification factors. Odds ratios and corresponding 95% confidence intervals and also confidence intervals of the differences in complication rates will be presented. Sensitivity analysis will be considered to account for missing data. The proportions of patients who have a 30-day and a 6-month post-operative complication which is solely related to trial specific interventions (e.g. related to the consent process and completion of questionnaires) will be summarised separately.

The differences in the proportion of patients who have died from any cause within the first 30 post-operative days between the treatment groups will be compared using logistic regression to adjust for the stratification factors. Odds ratios and corresponding 95% confidence intervals and also confidence intervals of the differences in 30-day operative mortality rates will be presented. Sensitivity analysis will be considered to account for missing data.

The differences in bladder and sexual function between the treatment groups at 6 months post-operation, as assessed by the patient self-reported I-PSS© and IIEF/FSFI© questionnaires, will be compared using adjusted for baseline mean scores and 95% confidence intervals for the overall symptom (bladder) and sexual function scores and for each individual I-PSS© item and sexual function domains, obtained from a multi-level repeated measures model adjusted for the stratification factors, assuming missing data at random. Missing data patterns will be examined and if missing data patterns suggest data are missing not at random, alternative analyses will also be carried out to allow for differing assumptions about the missing data (e.g. pattern-mixture modelling).

The differences in generic health-related quality of life and fatigue levels between the treatment groups at 30 days and 6 months post-operation, as assessed by the patient self-reported SF-36v2™ and MFI®-20 questionnaires, will be summarised using adjusted for baseline mean scores and 95% confidence intervals for the SF-36v2™ summary measures and MFI®-20 global fatigue scores and for each SF-36v2™ and individual fatigue scales, obtained from a multi-level repeated measures model adjusted for the stratification factors, assuming missing data at random and accounting for data at all time-points. Missing data patterns will be examined and if missing data patterns suggest data are missing not at random, alternative analyses will also be carried out to allow for differing assumptions about the missing data (e.g. pattern-mixture modelling).

Overall survival is defined as the time from date of randomisation to date of death from any cause; patients with missing follow-up data or who are still alive at the time of analysis, will be censored at the last date they were known to be alive. Disease-free survival is defined according to Punt et al's definitions26] as the time from date of randomisation to date of death from any cause, recurrent disease (locoregional or distant recurrence) or second primary cancer. Patients with missing follow-up data or who are alive and disease-free at the time of analysis will be censored at the date they were last known to be alive and disease-free. Kaplan-Meier curves for overall and disease-free survival will be calculated, and differences between the treatment groups at 3 years compared using Cox's proportional hazards model, if appropriate, to adjust for the stratification factors. Hazard ratios and corresponding 95% confidence intervals and also confidence intervals of the differences in 3-year overall and disease-free survival will be presented. Sensitivity analysis will be considered to account for missing data.

The differences between treatment groups in the quality of the plane of surgery, as assessed by the local histological review using the grading criteria given in Appendix 1, will be compared using ordered logistic regression to adjust for the stratification factors. Treatment estimates and corresponding 95% confidence intervals will be presented. Sensitivity analysis will be considered to account for missing data.

Subgroup analyses will also be performed to investigate the effect of the operation performed (high or low anterior resection or abdominoperineal excision) on outcomes.

To statistically assess the learning curve of robotic-assisted surgery, time-dependent factors known to influence the learning curve, such as the number of procedures performed in between randomised cases and prior to the first randomised patient and length of learning[31], will be incorporated into mixed-effects models as level 2 covariates, in addition to patient factors as level 1 covariates. To assess the impact that the learning curve may have on the interpretation of the results, analyses of only data from those surgeons with a lower than average conversion rate (or other outcome measure which is indicative of level of experience) will also be performed.

A Data Monitoring and Ethics Committee (DMEC) will be set up to independently review data on safety and recruitment. Interim reports will be presented to the DMEC in strict confidence, in at least yearly intervals. This committee, in light of the interim data, and of any advice or evidence they wish to request, will advise the Trial Steering Committee if there is proof beyond reasonable doubt that one treatment is better. No formal interim analyses are planned hence no statistical testing will take place until final analysis. Final analysis will take place in two stages when each patient has completed 1) 6 months of follow-up (for short-term outcomes) and 2) 3 years of follow-up.

14 Data Monitoring

Trial supervision will be established according to the principles of GCP and in line with the relevant Research Governance Framework within the UK (and any relevant research governance requirements in non-UK countries). This will include establishment of a core Project Team, Trial Management Group (TMG), a Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC).

14.1 Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee (DMEC) will be appointed to review the safety and ethics of the trial, alongside trial progress and the overall direction as overseen by the TSC. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals.

The DMEC will be provided with detailed unblinded reports containing the following information:

- Rates of occurrence of unexpected serious complications (USCs; see section 8.1) by treatment group
- Time between randomisation and surgery by treatment group for each participating site
- Rates of intra-operative conversion to open surgery by treatment group for each participating surgeon
- Rates of intra-operative and post-operative complications by treatment group for each participating surgeon
- Rates of circumferential resection margin positivity by treatment group for each participating surgeon

Trial progress will be closely monitored by the independent DMEC, who will report to the TSC, and the overall direction overseen by the TSC (ensuring regular reports to the EME programme). Particular attention will be paid to the rates of conversion, complications, and resection margin positivity as markers of safety. Any rates deemed to be excessive (conversion rates >50%; morbidity >50%; resection margin positivity >30%) will prompt further investigation and, if necessary, the suspension or withdrawal of individual sites or termination of the entire trial.

14.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU and the Spoke CTU. Missing data will be chased until they are received, until confirmed as not available, or until the trial is at analysis.

The CTRU or trial Sponsor will reserve the right to intermittently conduct source data verification (SDV) exercises on a sample of patients, which will be carried out by staff from

the CTRU or trial Sponsor or staff from the Spoke CTU (on behalf of CTRU or the trial Sponsor). SDV will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

A Trial Monitoring Plan will be developed.

14.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by patients during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual research sites.

15 Quality Assurance, Ethical Considerations, and Confidentiality

15.1 Quality Assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, the NHS Research Governance Framework (and any applicable research governance requirements in non-UK countries), and through adherence to CTRU SOPs.

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach that they become aware of. A serious breach of the protocol is classed as a serious breach which is made without permission as a result of error or fraud/misconduct. Minor protocol deviations are agreed with the Sponsor or CI either in advance or as soon as possible after the event.

In the event of any doubt, or for further guidance, the Investigator should contact the CTRU.

15.2 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000. Informed written consent will be obtained from the patients prior to randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

15.2.1 Ethical approval within the UK

Ethical approval in the UK will be sought through the National Research Ethics Service (NRES). The trial will be submitted to and approved by a main Research Ethics Committee (main REC) and the appropriate Site Specific Assessor for each participating site prior to entering patients into the trial. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant trial documentation.

15.2.2 Ethical approval outside the UK

For non-UK sites, it will be the contracted responsibility of the Principal Investigator at each site to ensure compliance to local standards of Clinical Governance and ethical approval. The relevant Spoke/Hub CTU (see section 17) will provide non-UK Principal Investigators

with a copy of the final protocol, patient information sheets, consent forms and all other relevant trial documentation, and will ensure country-specific ethical approval is established in accordance with the core protocol, and advise and supervise any permissible local amendments to accommodate local clinical trial legislation.

All non-UK Principal investigators will be required to provide the CTRU with a copy of the ethical approval document prior to patient recruitment and access to the randomisation system. Where relevant, this must be translated into English and signed and dated by the Principal Investigator.

15.3 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper at the CTRU (and/or the Spoke CTU). In addition, the CTRU will hold electronic information on all trial patients. The Spoke CTU will have controlled access to the trial database. The Spoke CTU will be issued with secure password protected access to patient data originating only from their affiliated research sites (see section 17). The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

The CTRU will comply with all aspects of the 1998 Data Protection Act and the Spoke CTU will be contractually required to comply with equivalent standards. Operationally this will include:

- Explicit written consent from patients to record personal details including name, date of birth, NHS number (for UK patients), hospital record number (outside UK).
- Appropriate storage, restricted access and disposal arrangements for patient personal and clinical details.
- Consent from patients for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- Consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.
- Copies of patient consent forms, which will include patient names, will be collected when a patient is randomised into the trial by the CTRU. All other data collection forms that are transferred to or from the CTRU or the other Spoke CTU will be coded with a unique patient trial number and will include two patient identifiers, usually the patient's initials and date of birth.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the patient's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a patient withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

15.4 Archiving

15.4.1 Trial data and documents held by CTRU and Spoke CTUs

At the end of the trial, data held on paper by the Spoke CTU will be securely transferred to the CTRU and all trial data will then be securely archived in line with the Sponsor's procedures for a minimum of 10 years.

15.4.2 Trial data and documents held by research sites

Research sites are responsible for archiving all trial data and documents (Investigator Site File and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

15.4.3 Patient medical records held by research sites

Research sites are responsible for archiving trial patient medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, patient medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

16 Statement of Indemnity

The University of Leeds will be liable for negligent harm caused to patients treated in the UK that is caused by the design of the trial.

The NHS has a duty of care to patients treated in the UK, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for harm to UK patients due to clinical negligence under this duty of care.

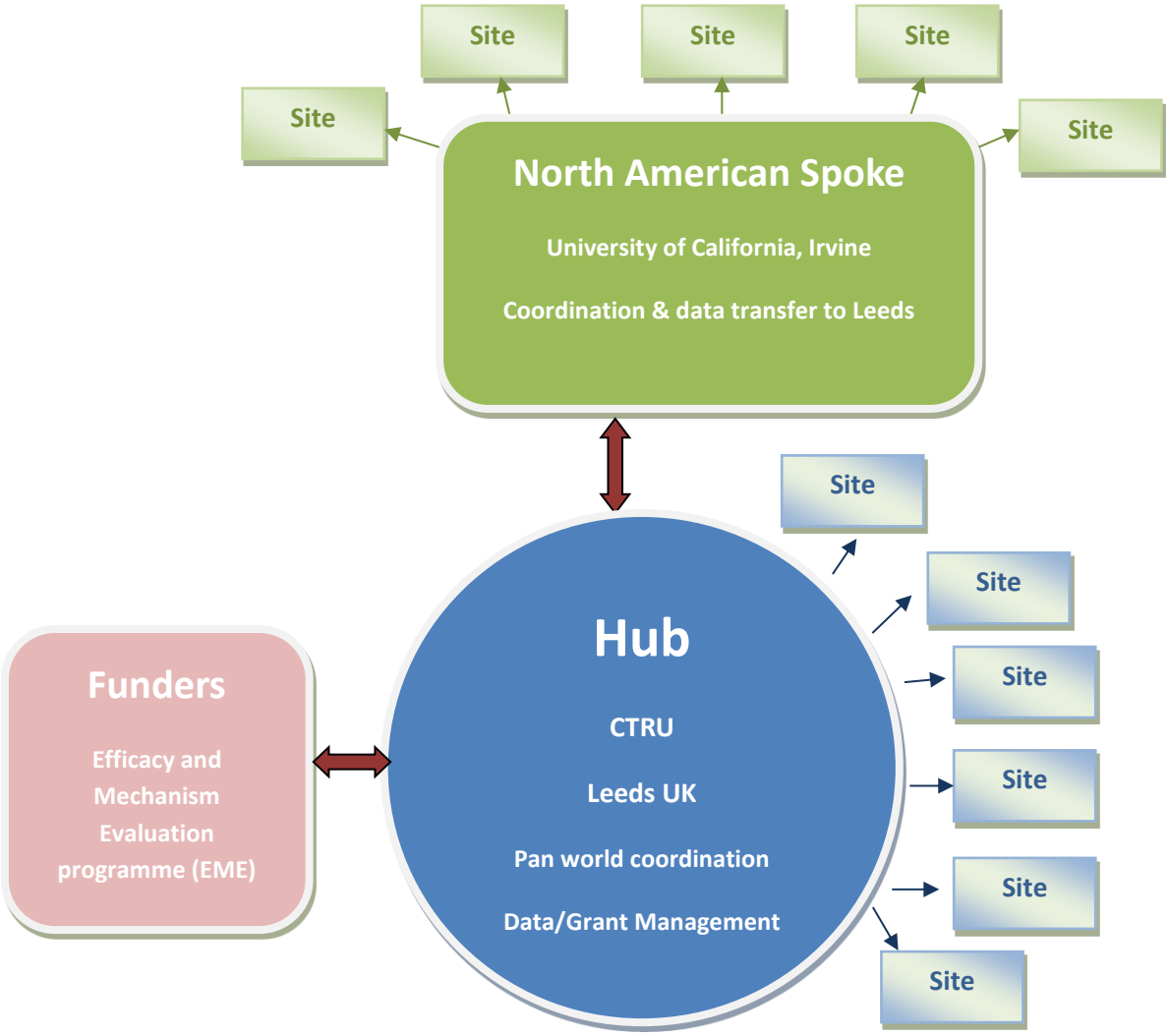
Research sites outside of the UK will be liable for clinical negligence and other negligent harm to patients under their care whether or not this arises as a result of trial-specific procedures.

17 Study Organisational Structure

To ensure strong pan-world coordination, the ROLARR trial will be set up on a "Hub-Spoke-Site" model (Figure 2), such that individual research sites in the USA feed into a regional Spoke CTU, which in turn feeds into the Hub CTU (CTRU) at the University of Leeds.

Research sites will liaise with their Spoke/Hub CTU for advice and support on trial operation, and submission of trial data. In turn, the Spoke CTU will be responsible for data chasing and transfer of data to the Hub CTU.

Figure 2: ROLARR Hub-Spoke-Site Model



17.1 Responsibilities

The Chief Investigator is responsible for the design, management and reporting of the trial.

As the Hub CTU, the CTRU will have responsibility for overall conduct of the trial in accordance with the Research Governance Framework and CTRU SOPs.

The Spoke/Hub CTUs will have delegated responsibility for the local conduct of the trial to all participating research sites in accordance with relevant local ethical approvals and regulatory procedures.

The responsibility for ensuring clinical management of patients is conducted in accordance with the trial protocol ultimately remains with the Principal Investigator at each research site.

17.2 Operational Structure

Chief Investigator: the Chief Investigator is involved in the design, conduct, co-ordination and management of the trial

Trial Management Group: the TMG, comprising the Chief Investigator, CTRU team, Spoke Clinical Lead, other key external members of staff involved in the trial, and a patient representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion
- CRF development
- Obtaining approval from the main REC and supporting applications for Site Specific Assessments (SSA)
- Completing cost estimates and project initiation
- Nominating members and facilitating the TSC and DMEC
- Reporting of serious adverse events
- Monitoring of screening, recruitment, treatment and follow-up procedures
- Auditing consent procedures, data collection, trial end-point validation and database development.

CTRU: the CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, ongoing management including training, monitoring reports and trial promotion, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any other site specific approvals, and clinical set-up for the sites for which it provides a Spoke CTU function. The CTRU will be responsible for the overall day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting, and all statistical analyses and pan-world trial coordination through delegation of appropriate responsibilities to the Spoke CTU.

Leeds Institute of Cancer and Pathology (LICAP): LICAP will take on responsibility for receipt, storage, processing/photographing, and return of slides, plus undertake central pathology QA review. LICAP will take sole responsibility for the receipt, storage, custodianship, and analysis of tumour/tissue blocks collected for future research. LICAP will also be responsible for appropriate anonymisation of all related pictures to be included on the LICAP Pathology website.

The Spoke CTU: the Spoke CTU will assume delegated responsibility for set-up and monitoring of trial conduct to CTRU SOPs (or equivalent), ongoing management including training, monitoring reports, promotion of the trial, support for ethical approval submissions and any other site specific approvals, and clinical set-up for their affiliated sites.

Trial Steering Committee (TSC): the TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. It will include an Independent Chair, not less than two other independent members, and a consumer representative. The Chief Investigator and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC): the DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment and follow-up. The Committee will meet annually as a minimum.

17.3 Funding

The research grant for this trial has been awarded by the Efficacy & Mechanism Evaluation (EME) programme which is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR).

18 Publication Policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines32], prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

In light of this, the Chief Investigator, Spoke Clinical Lead, other ROLARR grant applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators (surgeons and pathologists) will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. It is planned that the top five recruiting surgeons and pathologists will also be named as authors.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their patients which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint. Publications relating to methodological issues in ROLARR may be published prior to publication of the primary endpoint analysis.

On completion of the research project a draft final report will be submitted to the EME programme (trial funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the EME website. The CTRU is obliged to provide the EME programme with advanced notice of any publication relating to the trial. Copies of any materials intended for publication will be provided to the EME programme at least 28 days prior to submission for publication.

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20 Appendix 1: Pathological reporting

The pathology reporting in the ROLARR study is critical as one of the key secondary endpoints is CRM positivity. There is also an important role in identifying perforation and the planes of surgery of the mesorectum and the levator/anal sphincter, as well as response to neo-adjuvant therapy, lymph node involvement, extramural venous invasion and peritoneal involvement. For this study TNM5 is being used rather than TNM7 due to the poor reproducibility of the TNM7 definitions of tumour deposits. This therefore means that the 3 mm rule will be used for nodal involvement. This also allows this study to be consistent with other trials such as the MRC CLASICC trial, Dutch TME trial, CR07 etc.

In the recent MERCURY study[33], 31.9% of abdomino-perineal resections (APRs) vs 12% anterior resections (ARs) below 6 cm showed CRM positivity. This was also seen in the MRC CLASICC study[4] where 21% of APRs showed margin involvement vs 10% of ARs. In the Dutch TME/RT study[34] 30.4% of APRs had margin involvement vs 10.7% of ARs and in the Norwegian national audit of curative excisions of rectal cancer[35] 12% of APRs and 5% of ARs had positive margins. In series with follow-up, the increased rate of margin positivity always equated with an increased rate of local recurrence and a poorer survival. Thus when pathologically assessing APRs it is necessary to always look carefully for CRM positivity in the area of the low mesorectum and sphincter.

A higher rate of tumour perforation was also shown in APRs than in ARs in the Dutch study (13.7% of APRs were perforated vs 2.5% of ARs)[34] and in the Norwegian study (16% APRs vs 4% ARs)[35]. Abdomino-perineal resections have a higher rate of recurrence because of the smaller amount of tissues at the height of the levators and thought should be given to treating these as a high-risk category as the tumour is closer to the CRM. Their margin positivity rates are much higher and their survival worse than anterior resections. It should be recognised that the anatomy of the levator/anal canal area varies between individuals.

With this data it became apparent that there was a wide variation in the quality of the APR resections and a new quality classification was derived. This was similar to the mesorectal grading system in that it describes the surgical plane of dissection.

20.1 Preparation of the specimen

The specimen must be photographed prior to dissection. Preferably this is on receipt in the department. Digital photographs should be taken of the unopened front and back specimen, and cross sections of the specimen and preferably close up images of the front and back of the levator/anal sphincter (if appropriate).

The quality of the surgery should then be graded by the local pathologist for the mesorectum and the levator/anal sphincter area (as appropriate). The specimen can then be opened from the proximal margin down to 2-5 cms above the tumour. The distal end should be kept intact. If fresh material is to be taken for local use then it should be taken at this stage. A piece of foam/paper soaked in formalin can be inserted through the tumour if felt appropriate. The specimen can then be placed in formalin.

It is acceptable to inflate the specimen with formalin and then fix and take the photographs prior to dissection but this should be before opening the specimen. THE AREA OF THE TUMOUR MUST NEVER BE OPENED AS THIS DESTROYS THE ANTERIOR CRM.

20.2 Dissection

Anterior and posterior non-peritonealised surfaces are painted with ink. It should be remembered that the circumferential margin only applies to the surgically incised mesorectal planes and not the peritonealised surfaces. The mesorectal surface is larger posteriorly and extends up to a higher level than it does anteriorly. After the resection surfaces have been inked the specimen is fixed in formalin for a minimum of 2 days (48 hours).

The macroscopic description should be completed specifically noting the presence of a perforation at the tumour or distant from the tumour. It should be specifically stated whether the tumour perforation is present in an area covered by peritoneum or a surgical margin, and whether it is above or at the height of the sphincters. The presence or absence of levator ani on the specimen should be described. The descriptions of grading are given below.

The specimen should be sliced as thinly as possible starting from the distal margin to 2-5 cms above the tumour. These slices should be laid out in good light starting with the most distal slice at the top left hand corner and the most proximal slice ending up as the last slice. The face presented to the camera should be consistent in all the slices. These slices should then be photographed. The photograph must include a cm scale.

The minimum distance of the tumour to the CRM should be described, as should the maximum depth of invasion through the muscularis propria. If the CRM is free of tumour it should be noted whether there is normal tissue at the margin or whether it is fibrotic tissue following tumour regression.

If the CRM is involved (confirmed on histology) then the mode of involvement should be stated, as well as the minimum distance of involvement from the CRM. It is preferable to sample the main tumour by embedding each tumour bearing slice and cutting a large mount section. As many lymph nodes as possible should be dissected and a running mean of at least fifteen is to be expected in cases not undergoing preoperative neo-adjuvant therapy.

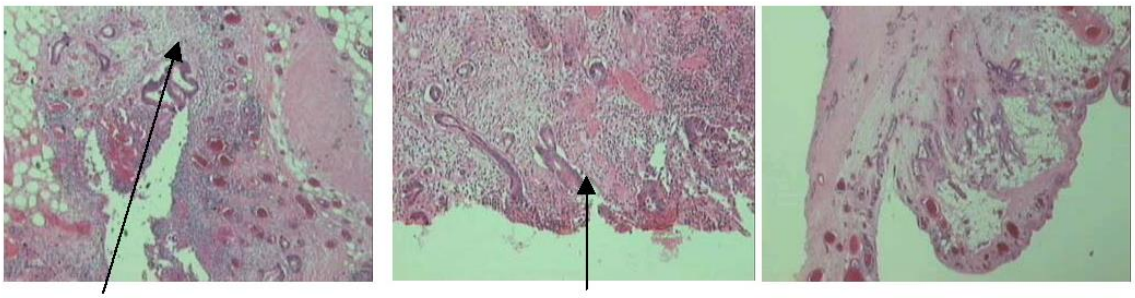
Involvement of the peritoneum is defined as per Shepherd et al[36] and extramural vascular invasion when involvement of a vascular structure with smooth muscle in the wall is apparent. This should be looked for closely and if tumour is present close to an arterial structure without an accompanying vein have a high level of suspicion. Involvement of the CRM is defined as tumour within 1 mm of the CRM. If the tumour is at the margin then the case is R1; if the tumour is within 1 mm but not at the margin then it is an R1<1mm according to the revised R1 guidelines.

See sections 7.5.2 and 7.5.3 of the protocol for procedures for central slide review and optional tissue donation.

20.3 T staging of low rectal cancers

The T-staging of cancers above the sphincters is straightforward, however many of these cancers have a proportion of the lesion within the region of the sphincters. T staging of adenocarcinoma in the area of the sphincters is unsound. TNM 6 states that such tumours should be staged as anal cancers by tumour size. In TNM 7 this did not change. In the absence of a robust staging system the only solution is to describe the anatomical extent of spread both above the sphincter and at their height separately to allow subsequent analysis.

We propose that the maximum level of invasion above the sphincter and at the level of the sphincter be separately recorded by extent of maximal spread.



Peritoneal involvement with tumour penetrating the peritoneum

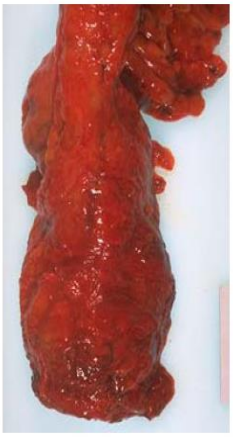
20.3.1 Assessment of Quality of Surgery – Grading

The mesorectum and the levator canal should be graded separately. Thus for an anterior resection (AR) there will only be one grade (mesorectum). For abdomino-perineal resections (APR) there will be a grade for the mesorectum and a further grade for the levator canal area below the mesorectum.

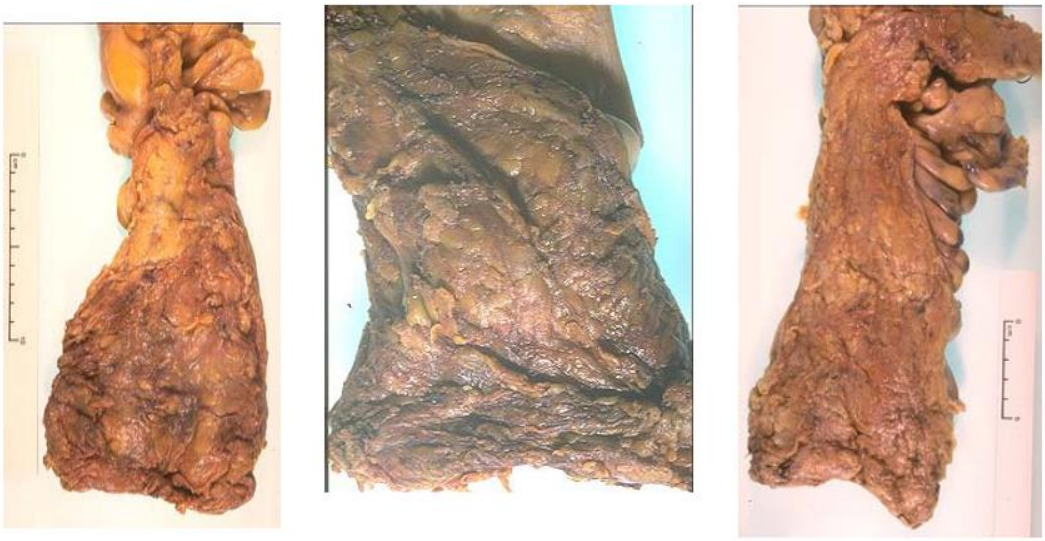
20.3.2 Quality of resection of the mesorectum

The quality of a mesorectal resection can be easily assessed.

Mesorectal fascial plane: the mesorectum should be smooth with no violation of the fat, good bulk to the mesorectum anteriorly and posteriorly and the distal margin should appear adequate with no coning near the tumour. No defect should be more than superficial or 5mm deep.



Intramesorectal plane: Moderate bulk to mesorectum but irregularity of the mesorectal surface. Moderate coning of the specimen towards the distal margin. At no site is the muscularis propria visible with the exception of the area of insertion of levator muscles. Moderate irregularity of the CRM. See images below with superficial incursions into the mesorectum, areas of mesorectum missing, coning of the mesorectal dissection and most importantly in no area is the muscularis propria exposed.



Intramesorectal plane

Superficial incisions **Superficial incisions and coning** **Coning**

Muscularis propria plane: There will be areas of substantial loss of mesorectal tissue. Deep cuts and tears down onto the muscularis propria will be present. On cross section there will be a very irregular CRM with little bulk to the mesorectal fat and the muscularis propria will form the CRM in places.

This classification has been used in the CR07 and CLASICC trials and shown to predict a higher risk of local recurrence in the Dutch data. The frequency of CRM involvement can also be determined and it is likely that this is a good early determinant of the quality of surgery and subsequent risk of local recurrence. The ease of high quality surgery after chemoradiotherapy also needs to be determined.

Muscularis propria surgery

–irregular mesorectum with defects > 1 cm^2 or incision down to muscularis propria.

Irregular CRM with little bulk and little clearance anteriorly

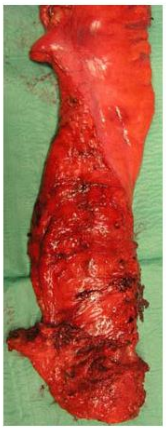
20.3.3 Quality of resection (abdomino-perineal resection only)

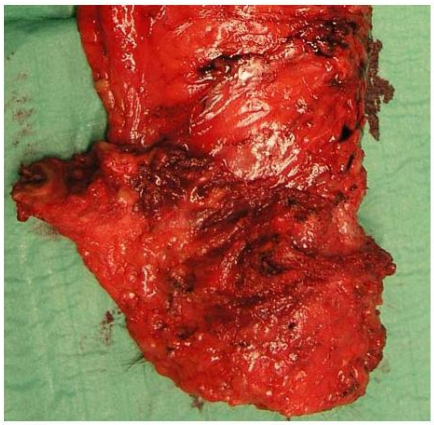
Thus the quality of surgery of the levator/anal canal area below the mesorectum can be assessed as:

Levator plane (attached to mesorectum)

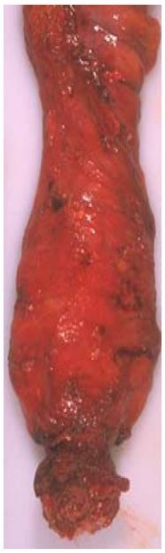
The surgical plane lies external to the levators with them being removed *en bloc* with the specimen. This creates a cylindrical specimen with the levators forming an extra protective layer on the sphincters.

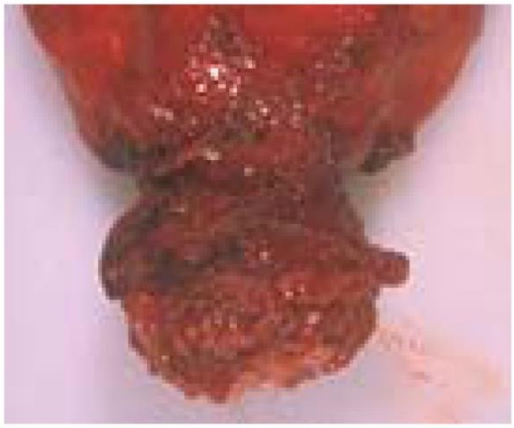
Levator plane





Sphincteric plane: Either there are no levator muscles attached to the specimen or only a very small cuff and the resection margin is on the surface of the sphincters.

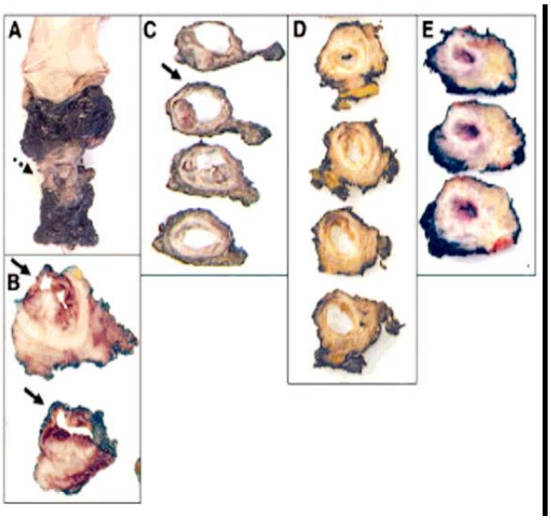




Intrasphincteric/submucosal/perforation plane: The surgeon has inadvertently entered the sphincters or even deeper into the submucosa or perforated the specimen at any point.

Intrasphincteric/submucosal plane: APE with areas of failure to excise all of the muscularis propria in the area of the levators and no levator excision.

Cross sections of AP



A, : Perforation B,C /submucosaD: Sphincter E levator

Thus for an AR there will be a single grade and for an APR there will be two grades.

20.4 Chemoradiotherapy response scoring

Dworak scoring[37]:

1. **No regression detectable**.
2. **Minimal regression:** dominant tumour mass with obvious fibrosis and/or vasculopathy.
3. **Moderate regression:** dominantly fibrotic changes with few tumour cells or groups (easy to find).
4. **Good regression:** very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucin.
5. **Total regression:** no tumour cells, only fibrotic mass or mucin.

20.5 Assessment of specimens where tumour cells are difficult to find

Where tumour cells cannot be found on the first assessment of five blocks of tumour the whole area of the tumour will be embedded. Should no further tumour cells be seen then three levels will be taken and examined from each tumour block. If after these assessments no tumour cells are identified then the tumour should be considered to have undergone a complete response. Further levels should not be taken as it is important to standardise the degree of effort made to find the presence of tumour.

20.6 Definitions used in Pathology

20.6.1 Position of the tumour

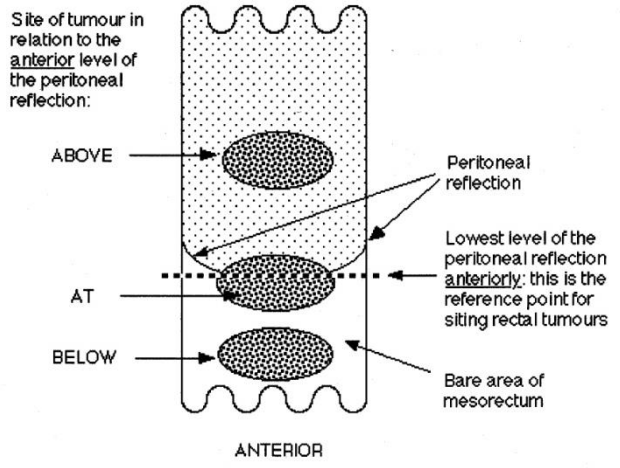
The position of the tumour should be accurately noted. Initially this involves documentation of the surface involvement – i.e. anterior quadrant, posterior quadrant, lateral quadrant and combinations of the above. However, to correlate the position with the MRI report the tumour should be reported from the distal resection margin with the mesorectum posterior and the peritoneal reflection anterior. This can be documented as a relationship to a clock-face on the reporting proforma.

ALL POSITIONS SHOULD BE REPORTED FROM THE PATIENTS PERSPECTIVE TO CORRELATE WITH THE MRI.

20.6.2 Relationship to the peritoneal reflection

The crucial landmark for recording the site of rectal cancers is the peritoneal reflection. This is identified from the exterior surface of the anterior aspect of the specimen. Rectal cancers are classified according to whether they are:

1. Entirely above the level of the peritoneal reflection anteriorly
2. Astride (or at) the level of the peritoneal reflection anteriorly
3. Entirely below the level of the peritoneal reflection anteriorly



20.6.3 Relationship to the CRM

Anteriorly the upper rectum is covered by peritoneum. Only the area below the peritoneal reflection is at risk of surgical circumferential margin involvement. Posteriorly this area, and the area above it, a triangular shaped bare area running up to the start of the sigmoid mesocolon, is at risk not only from direct tumour spread but also metastatic deposits in lymph nodes that lie against the circumferential margin.

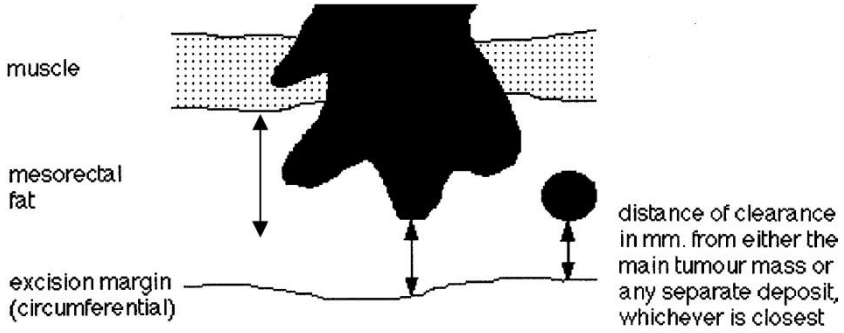
It is recommended that the whole of this margin (i.e. the mesorectum) be painted with a marker such as silver nitrate or India Ink before dissecting the specimen. The tumour is then best sliced serially at 3-4 mm intervals to select blocks from the area above and below the tumour to look for metastatic deposits. If lymph nodes lie against the circumferential margin then these should be included in the block.

20.6.4 Relationship to extra-mural invasion

When assessing the relationship to the CRM, on the whole-mount section the corresponding relationship between the outer muscle coat and the maximum depth of extra-mural invasion needs to be measured. This is performed using the Vernier scale on the microscope.

20.6.5 Lymph nodes

All lymph nodes found in the specimen should be sampled and counted, regardless of their site and size. The number of positive lymph nodes must be equal to or less than the number of lymph nodes sampled.



Extramural tumour deposits measuring ≥ 3 mm are counted as involved lymph nodes even if no residual lymph node structure can be identified. Smaller deposits are regarded as apparent discontinuous extensions of the main tumour.

In the TNM staging system, pN1 corresponds to involvement of 1-3 nodes and pN2 to involvement of 4 or more nodes.

20.6.6 Distance to the distal resection margin

Measured from the nearest cut-end of the specimen, not the circumferential margin. It is only necessary to examine the margins histologically if tumour extends macroscopically to within 30 mm of one of these. For tumours further than be assumed that the cut ends are not involved. Exceptions to this recommendation are adenocarcinomas that are found on subsequent histology to have an exceptionally infiltrative growth pattern or show extensive vascular or lymphocyte permeation or are undifferentiated carcinomas.

20.6.7 Relationship to the dentate line

This can only be measured for low rectal tumours in abdomino-perineal excision of the rectum (APR) specimens. The dentate line should be defined as the level of the limit of the internal sphincter.

If the tumour has perforated into the peritoneal cavity or is clearly present in tissue beyond the edge of the mesorectal fascia then these cases should be recorded as a perforation.

20.6.8 Tumour differentiation

The differentiation of the tumour should be defined on the dominant area of tumour. Other types of differentiation, i.e. mucinous adenocarcinomas, signet ring and undifferentiated should be documented.

21 Appendix 2: ASA Physical Status Classification System[38]

1 A normal healthy patient

2 A patient with mild systemic disease

3 A patient with severe systemic disease

4 A patient with severe systemic disease that is a constant threat to life

5 A moribund patient who is not expected to survive without the operation

6 A declared brain-dead patient whose organs are being removed for donor purposes

22 Appendix 3: Abbreviations Used

APR	Abdomino-perineal resection
AR	Anterior resection
ASA	American Society of Anaesthetists
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case report form
CRM	Circumferential resection margin
CTRU	Clinical Trials Research Unit
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DVT	Deep vein thrombosis
EME	Efficacy and Mechanisms Evaluation
EQ-5D	EuroQol-5 Dimensions
FSFI	Female Sexual Function Index
GCP	Good Clinical Practice
ICER	Incremental cost-effectiveness ratio
IIEF	International Index of Erectile Function
IMA	Inferior mesenteric artery
IMV	Inferior mesenteric vein
I-PSS	International Prostatic Symptom Score
ISF	Investigator site file
ITT	Intention to treat
MFI-20	Multi-dimensional Fatigue Inventory-20
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NHS	National Health Service (UK)
NIHR	National Institute for Health Research (UK)
NRES	National Research Ethics Service (UK)
PI	Principal Investigator
PPI	Patient and public involvement
PRO	Patient reported outcomes
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of Life
REC	Research Ethics Committee
SDV	Source data verification
SF-36v2	Short-Form 36 version 2
SOP	Standard operating procedure
SSA	Site Specific Assessment (UK)
TME	Total mesorectal excision
TMG	Trial Management Group
TSC	Trial Steering Committee
USC	Unexpected Serious Complication

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