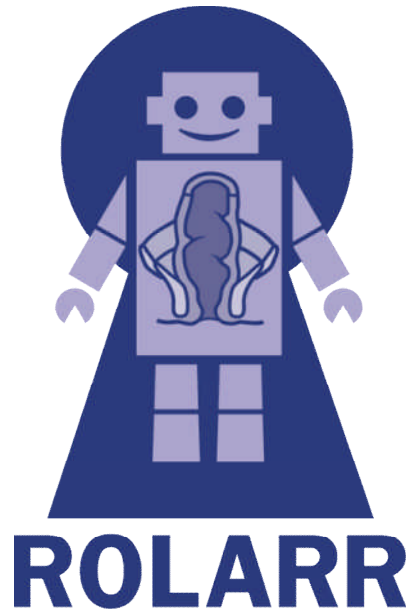


16-05328 - Short-Term Results from the Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) Trial Supplement

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.



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

**Chief Investigator
and European Spoke Lead:**

Mr David Jayne
Senior Lecturer in Surgery
Academic Unit of Medicine, Surgery & Anaesthesia
University of Leeds
Level 7 Clinical Sciences Building
St James's University Hospital
Leeds LS9 7TF

North American Spoke Lead:

Professor Alessio Pigazzi
Assistant Clinical Professor of Surgery
City of Hope National Medical Center
California, USA

South East Asian Spoke Lead:

Professor Charles Tsang
Research Professor of Surgery
Division of Colorectal Surgery
University of Singapore

Key Contacts

Chief Investigator:

Mr David Jayne
Senior Lecturer in Surgery
Academic Unit of Medicine, Surgery & Anaesthesia
University of Leeds

Tel: +44 113 206 5218
Fax: +44 113 244 9168
Email: djayne@leeds.ac.uk

Trial Management:

Dr Helen Howard
Head of Trial Management - Solid Tumours
Clinical Trials Research Unit
University of Leeds

Tel: +44 113 343 2657
Fax: +44 113 343 1471
Email: h.c.howard@leeds.ac.uk

Dr Sue Pavitt
Director of Comprehensive Health Research Division
Clinical Trials Research Unit
University of Leeds

Tel: +44 113 343 8609
Fax: +44 113 343 1471
Email: s.pavitt@leeds.ac.uk

Statistics:

Miss Helen Thorpe
Principal Statistician
Clinical Trials Research Unit
University of Leeds

Tel: +44 113 343 1481
Fax: +44 113 343 1471
Email: h.c.thorpe@leeds.ac.uk

Professor Julia Brown
Director of Clinical Trials Research Unit
Clinical Trials Research Unit
University of Leeds

Tel: +44 113 343 1477
Fax: +44 113 343 1471
Email: j.m.b.brown@leeds.ac.uk

Clinical Fellow:

Dr Fiona Collinson
Clinical Lecturer (Oncology and Clinical Trials)
Clinical Trials Research Unit
University of Leeds

Tel: +44 113 343 1491
Fax: +44 113 343 1471
Email: f.j.collinson@leeds.ac.uk

Health Economics:

Professor Chris McCabe
Professor of Health Economics
Academic Unit of Health Economics
University of Leeds

Tel: +44 113 343 6989
Fax: +44 113 343 3470
Email: c.mccabe@leeds.ac.uk

Dr Richard Edlin
Lecturer in Health Economics
Academic Unit of Health Economics
University of Leeds

Tel: +44 113 343 0879
Fax: +44 113 343 3470
Email: r.p.edlin@leeds.ac.uk

Pathology:

Professor Phil Quirke
Professor of Pathology
Section of Pathology and Tumour Biology
University of Leeds

Tel: +44 113 343 8407
Fax: +44 113 343 8431
Email: p.quirke@leeds.ac.uk

International Clinical Leads:

Professor Alessio Pigazzi
Assistant Clinical Professor of Surgery
City of Hope National Medical Center
California, USA

Tel: +1 626 471 7100
Fax: +1 626 301 8865
Email: APigazzi@coh.org

Professor Charles Tsang
Research Professor of Surgery
Division of Colorectal Surgery
University of Singapore

Tel: +65 67724235
Email: ctsang@nuh.sg

Surgical Advisor:

Professor Pierre Guillou
Professor of Surgery
c/o Leeds Institute of Molecular Medicine
Level 7 Clinical Sciences Building
St. James's University Hospital
Leeds LS9 7TF

Tel: +44 113 206 5281
Fax: +44 113 244 9618
Email: p_guillou@hotmail.com

Patient Advisor:

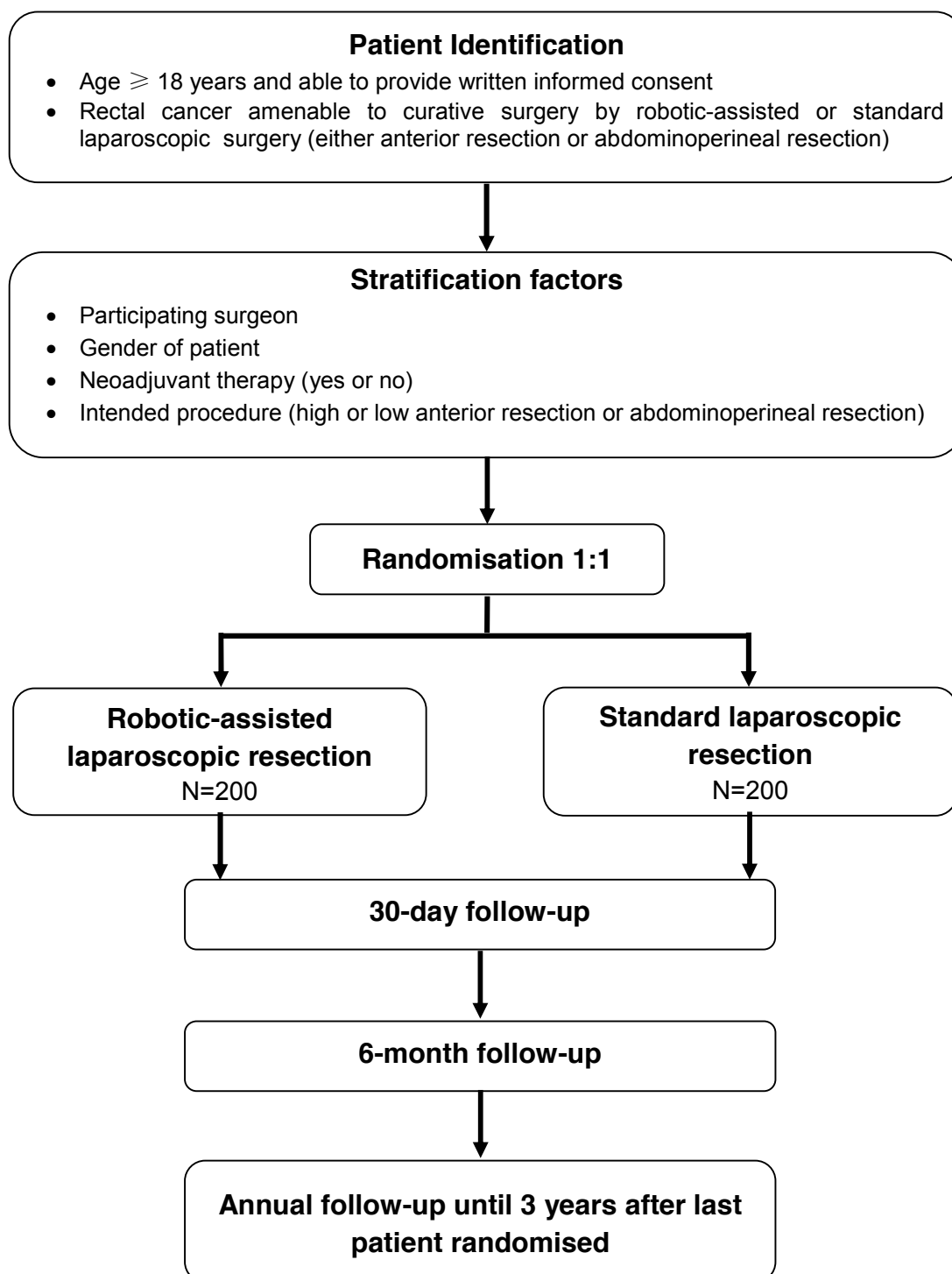
Mr Christopher Garbett

Contents

1	TRIAL SUMMARY	1
2	BACKGROUND	2
	2.1 EXISTING RESEARCH.....	2
	2.2 RISKS AND BENEFITS	3
	2.3 RATIONALE FOR CURRENT STUDY.....	4
	2.4 AIMS AND OBJECTIVES.....	4
3	DESIGN.....	5
4	ELIGIBILITY.....	5
	4.1 PATIENT ELIGIBILITY.....	5
	4.2 SITE ELIGIBILITY	6
	4.3 SURGEON ELIGIBILITY	6
5	RECRUITMENT AND RANDOMISATION OF PATIENTS.....	6
	5.1 RECRUITMENT OF PATIENTS.....	6
	5.2 RANDOMISATION.....	7
	5.3 NON-RANDOMISATION	8
6	INTERVENTION DETAILS	9
	6.1 PRE-OPERATIVE INVESTIGATION AND PREPARATION	9
	6.2 SURGERY.....	9
	6.3 POST-OPERATIVE CARE.....	9
	6.4 WITHDRAWAL OF TREATMENT.....	9
7	ASSESSMENT AND DATA COLLECTION	10
	7.1 SUBMISSION OF TRIAL DATA	10
	7.2 SCHEDULE OF EVENTS.....	10
	7.3 PRE-OPERATIVE ASSESSMENTS AND DATA COLLECTION	13
	7.4 OPERATIVE ASSESSMENTS AND DATA COLLECTION	13
	7.5 PATHOLOGY ASSESSMENT	13
	7.6 POST-OPERATIVE ASSESSMENT AND DATA COLLECTION.....	15
	7.7 FOLLOW-UP ASSESSMENT AND DATA COLLECTION	15
	7.8 DEATH.....	15
	7.9 ASSESSMENT OF SURGICAL SKILLS	16
	7.10 QUALITY OF LIFE AND HEALTH ECONOMIC ASSESSMENT.....	16
8	SAFETY REPORTING.....	16
	8.1 GENERAL DEFINITIONS.....	16
	8.2 ROLARR EXPECTED COMPLICATIONS.....	18
	8.3 REPORTING OF COMPLICATIONS	19
	8.4 DEATHS	19
	8.5 RESPONSIBILITIES FOR SAFETY REPORTING	20
	8.6 REPORTING	21
9	QUALITY OF LIFE.....	21
10	ECONOMIC EVALUATION	22

11	ENDPOINTS.....	23
11.1	PRIMARY ENDPOINT	23
11.2	SECONDARY ENDPOINTS.....	23
12	STATISTICAL CONSIDERATIONS	24
12.1	SAMPLE SIZE	24
13	STATISTICAL ANALYSIS.....	26
14	DATA MONITORING	28
14.1	DATA MONITORING AND ETHICS COMMITTEE	29
14.2	DATA MONITORING	29
14.3	CLINICAL GOVERNANCE ISSUES.....	29
15	QUALITY ASSURANCE, ETHICAL CONSIDERATIONS, AND CONFIDENTIALITY	30
15.1	QUALITY ASSURANCE	30
15.2	ETHICAL CONSIDERATIONS.....	30
15.3	CONFIDENTIALITY.....	30
15.4	ARCHIVING	31
16	STATEMENT OF INDEMNITY.....	31
17	STUDY ORGANISATIONAL STRUCTURE	32
17.1	RESPONSIBILITIES.....	32
17.2	OPERATIONAL STRUCTURE.....	32
17.3	FUNDING	33
18	PUBLICATION POLICY	34
19	REFERENCES	35
20	APPENDIX 1: PATHOLOGICAL REPORTING	36
20.1	PREPARATION OF THE SPECIMEN	36
20.2	DISSECTION	37
20.3	T STAGING OF LOW RECTAL CANCERS	37
20.4	CHEMORADIOTHERAPY RESPONSE SCORING.....	41
20.5	ASSESSMENT OF SPECIMENS WHERE TUMOUR CELLS ARE DIFFICULT TO FIND	41
20.6	DEFINITIONS USED IN PATHOLOGY	41
21	APPENDIX 2: GLOBAL RATING SCALE COMPONENT OF THE INTRAOPERATIVE ASSESSMENT TOOL (GOALS)* [19]	44
22	ABBREVIATIONS USED.....	45

1 Trial Summary



2 Background

2.1 Existing research

The feasibility and safety of laparoscopic surgery has been established for colon cancer[1,2,3]. 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[5] or 5-year follow-up (submitted for publication). 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 [12].

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[11]. 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 [12]. 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 in participating in this trial, above that normally associated with routine clinical practice. The clinical indications and contraindications 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 (Intuitive Surgical, Sunnyvale, USA). 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; evaluation of intra-operative laparoscopic skills (GOALS)).

4 Eligibility

4.1 Patient eligibility

4.1.1 Inclusion criteria¹

1. Aged ≥ 18 years
2. Able to provide written informed consent
3. Diagnosis of rectal cancer² amenable to curative surgery either by anterior resection or abdominoperineal resection (i.e. staged T1-3, N0-2, M0 by CT and MRI or transrectal ultrasound)
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. ASA ≤ 3
7. Capable of completing required questionnaires at time of consent

4.1.2 Exclusion criteria

1. Benign lesions of the rectum
2. Cancers 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

¹ Please note that patients of any BMI are eligible

² Rectal cancer is defined as a distal tumour <15 cm from the anal verge measured by rigid sigmoidoscopy.

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
11. Participation in another rectal cancer clinical trial relating to surgical technique

4.1.3 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.

4.1.4 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 CTRU 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 either robotic-assisted or 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.

4.3 Surgeon Eligibility

All participating surgeons must have performed a minimum of 10 robotic rectal cancer resections prior to trial participation, and must have at least equivalent experience of performing standard laparoscopic surgery.

5 Recruitment and Randomisation of Patients

5.1 Recruitment of Patients

A total of 400 patients (200 in each arm) will be recruited into the trial over an 18-month period. It is anticipated that approximately 15 patients per month will be recruited in the first

6 months, with monthly recruitment increasing to approximately 25 patients in the final 12 months.

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) and 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 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). Patient consent and randomisation must take place as close to the date of surgery as possible and at most no more than 14 days before surgery; however, it is recognised that this may not always be possible, and therefore up to 28 days may be required depending on the local situation. This will be monitored by the DMEC.

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
- 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).

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
- Ethnicity
- 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 CTU.

6 Intervention Details

6.1 Pre-operative investigation and preparation

Preoperative investigation and preparation will be as per institutional protocol. It is strongly advised that all patients are fully assessed preoperatively by CT scan and MRI or transrectal ultrasound scan.

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 (\pm 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. Sites will keep copies of all completed CRFs for the trial within the ISF.

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 three international Spoke CTUs:

- European spoke CTU: CTRU, University of Leeds, UK
- North American Spoke CTU: Hope Hospital CTU, California, USA
- South East Asian Spoke CTU: National University Hospital CTU, Singapore

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 CTUs in California and Singapore.

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 (pre-randomisation)	Pre- surgery	Surgery	Pathology Review	Hospital stay	30 d Post-op clinical review ¹	6 m Post-op clinical review ²	Annual status review ³
Medical Assessment	X						X	X	X
Pre-op investigations ⁴	X								
Pregnancy test ⁵	X								
Eligibility CRF	X								
Informed Consent	X								
EQ5D ⁶		X					X	X	
Bladder and sexual function questionnaires (IPSS and IEF/FSFI)		X						X	
QoL questionnaire (SF-36)		X					X	X	
Fatigue questionnaire (Multi- dimensional Fatigue Inventory MFI-20)		X					X	X	
Patient reported questionnaires related to resource utilisation ⁶							X	X	
Randomisation CRF			X						
Randomisation			X ⁷						
Surgery				X ⁷					
Video of the mesorectal dissection				X ⁸					
Photograph of specimen ⁹					X				
Histopathological examination of specimen ¹⁰					X				
Histopathology CRF					X				
Operative CRF				X					
30 day review CRF							X		
6 month review CRF								X	
Annual follow-up CRF									X
Complications ¹¹		X	X	X		X	X	X	
Expedited reporting (<24 h) of unexpected serious complications (USCs) ¹²		← X →							

First post-operative clinical review must not take place earlier than 30 days, but may take place up to 37 days post-operatively.

² Second post-operative clinical review should take place 6 months \pm 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 transrectal ultrasound scan at a minimum

⁵ In women of child bearing potential a pregnancy test must be negative within 72 hrs of the operation

⁶ In U.K. and North America only

⁷ 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.

⁸ Sites will be required to submit a video of at least 1 hour of the mesorectal dissection from randomly selected cases (reflecting those recruited early and late at each site) inclusive of both robotic-assisted and standard laparoscopic operations (see section 7.9).

⁹ Photographs of the front and back and cross section of the 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 tape measure should be visible to enable the size to be recorded.

¹⁰ Resection pathology specimens will be reported using standard methods [18] (fields defined on histopathology CRF)

¹¹ 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 \leq 30 days post-operatively and including any pre-operative complications 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.

¹² 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 BMI and gender
- Date of diagnosis³
- 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

Patients will also be asked to complete the baseline generic health-related QoL and fatigue questionnaires (SF-36 and MFI-20), EQ-5D, health economic patient reported medical resource utilisation questionnaires and patient reported bladder and sexual function questionnaires (IPSS and IIEF/FSFI) 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
- 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 [18]. Further details are provided in Appendix 1.

³ The date of diagnosis is defined as the date of pathological confirmation.

| 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 surgical excision (mesorectal, intramesorectal or muscularis propria for mesorectum and extralevator, sphincteric or intrasphincteric/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, tissue 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

Digital photographs of the anterior, posterior 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 tape measure to enable sizing of the specimen.

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

- Unique trial number
- Initials
- Date of birth
- Histopathology report number

To enable central pathological review a digital copy of slide (or if not possible a specimen sample such as, the original slides, a duplicate slide, or block) will need to be collected. This is to enable international consistency in reporting of the CRM and TM v5. If original slides are sent they will be scanned and returned.

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

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

7.7 Follow-up Assessment and Data Collection

A 6 month (\pm 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.

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 diagnosis⁴
- Details of any new primary cancer diagnoses

At the 6 month post-operative visit only, data relating to complications will also be collected and patients will also complete appropriate questionnaires (SF-36, MFI-20, EQ-5D, patient reported questionnaires related to resource utilisation, IPSS 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

⁴ Disease recurrence (local or distance) may be initially detected by radiological follow-up, but should be confirmed by tissue biopsy where possible.

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 Assessment of Surgical Skills

It is suggested that robotic-assistance results in decreased operator fatigue, which may affect conversion rates and improve oncological outcomes. To assess this, a global assessment tool for evaluation of intraoperative laparoscopic skills, the Global assessment tool for evaluation of intraoperative laparoscopic skills (GOALS) score [19], will be incorporated. Sites will be required to submit (to the CTRU) a video of at least 1 hour of the mesorectal dissection from randomly selected cases (reflecting those recruited early and late at each site) inclusive of both laparoscopic and robotic operations. Videos will be reviewed by an independent expert blind to the surgeon and surgery performed, and used to assign a GOALS score. GOALS data will also prove useful in assessing technical competency and determining any learning curve effect.

7.10 Quality of Life and Health Economic Assessment

The EQ-5D, generic health-related quality of life (SF-36) 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 (IPSS, 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).

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 procedures directly related to the surgery (e.g. anaesthetic) 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:

17 | R O L A R R

- results in death
- is life-threatening⁵
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- 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) 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 not listed in the protocol as an expected occurrence (see section 1.1)

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.

⁵ 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

- Altered bowel habit
- Anastomotic leak
- Gastrointestinal fistula
- Gastrointestinal ischaemia/necrosis
- Gastrointestinal obstruction
- Gastrointestinal perforation
- Gastrointestinal stricture/stenosis
- Gastrointestinal ulceration
- Haemorrhage
- Hernia
- Ileus
- Intra-abdominal/pelvic abscess
- Post-operative peritonitis
- Sexual dysfunction
- Stoma prolapse/necrosis
- Urinary dysfunction
- Urinary retention
- Wound infection
- Wound dehiscence

Cardiorespiratory

(May be operative or post-operative)

- Respiratory, including
 - Acute respiratory distress syndrome/respiratory failure
 - Aspiration
 - Atelectasis
 - Bronchospasm
 - Pleural effusion
 - Pneumonia/chest infection
 - Pulmonary embolus (or DVT)
- Cardiac, including
 - Arrhythmia
 - Cardiac failure
 - Ischaemic heart disease/myocardial infarction
- Cardio-respiratory arrest

Other

- Acute renal failure
- Back pain
- Cerebrovascular attack/stroke
- Disseminated intravascular coagulation
- Distal limb ischaemia/compartment syndrome
- Metabolic acidosis
- Necrotising fasciitis
- Pressure sore
- Pseudomembranous colitis
- Scrotal swelling
- Sepsis
- Subcutaneous emphysema
- Urinary tract infection
- Delirium

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 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 1487

For each USC, the following data will be collected:

- Start and end dates of event, if resolved (and times, if known/applicable)
- Full details of complication in medical terms with a diagnosis (if possible)
- Action/intervention
- Outcome

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.

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 on the operative CRF, 30 day post-operative CRF or 6 month post-operative CRF, as appropriate.

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 consent 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 local co-

ordinating Spoke CTU within 7 days of the research staff becoming aware of the event. The original form should then be posted to the Spoke 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 CTU.

8.5 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 are recorded and reported to the CTRU (hub) within 24 hours of the clinical research staff becoming aware and to provide further follow-up information as soon as available.
- To report USCs to local co-ordinating 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 but not 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.

International Spoke CTUs

- Ensure adherence to local (country-specific) safety reporting arrangements

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.

8.6 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 (IPSS) 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 [20]. To assess sexual function, the International Index of Erectile Function (IIEF) [21] and Female Sexual Function Index (FSFI) [22] 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 IPSS, 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 SF36, 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 [23]. 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 prior to randomisation (randomisation should take place immediately following completion of baseline questionnaires). Patients will be asked to also complete the SF36, 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 pre-supplied stamped addressed envelopes prior to being given to research staff. Research staff will then send the sealed envelopes to the Spoke 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 robot (Intuitive Surgical, Sunnyvale, USA). 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 [24]. 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 ≤ 1 mm 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 recurrence⁶. 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 IPSS 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-36 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 [25] as the time from date of randomisation to date of death from any cause, recurrent disease (locoregional or distant recurrence) or second primary cancer⁵.
- Health economics:
 - Preference based QoL measured by EQ-5D and used to calculate quality-adjusted life-years (QALYs).
 - Direct resource utilisation

⁶ The date of recurrence is defined as the date of radiological or pathological confirmation, whichever occurs first.

- Cost-effectiveness estimated using QoL and direct resource use information combined with apportioned cost scenarios of the robotic device.
- Intra-operative laparoscopic skills (randomly selected cases only) as assessed by an independent expert blind to surgeon and surgery performed using the global assessment tool for evaluation of intra-operative laparoscopic skills 'GOALS' [19], using the grading criteria given in Appendix 2.
- Quality of the plane of surgery as assessed by central review of photographs, blind to surgeon and surgery performed, 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%²; a more realistic and current conversion rate for a group of experienced laparoscopic surgeons would be ~25% [26]. 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, 27]. 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). 400 patients (200 per arm) will therefore be recruited to allow for early withdrawals, cross-over, protocol violations (e.g. benign tumours) and missing follow-up data.

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 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 [28], as adopted in the MRC CLASICC trial². 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 [29], the table indicates that 400 patients will be sufficient to be able to reliably answer this question.

Table 2: Likely widths of the 95% CI for various absolute differences in the CRM positivity rates

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 [5] 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% [5], 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. As detailed in section 5.1, recruitment is expected to be slower in the first 6 months; it is anticipated that approximately 15 patients per month will be recruited in the first 6 months, with recruitment increasing to approximately 25 patients per month in the final 12 months.

Table 3: Likely widths of the 95% CI for various absolute differences in the 3-year local recurrence rates

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.

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 ≤ 1 mm 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 IPSS 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 IPSS 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-36 and MFI-20 questionnaires, will be summarised using adjusted for baseline mean scores and 95% confidence intervals for the SF-36 summary measures and MFI-20 global fatigue scores and for each SF-36 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 definitions [25] 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 intra-operative laparoscopic skills, as assessed by the global assessment tool for evaluation of intra-operative laparoscopic skills 'GOALS', will be summarised descriptively for the overall GOALS score and for each component item.

The differences between treatment groups in the quality of the plane of surgery, as assessed by the central review of the specimen photographs 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 [30], 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 analyses will be presented to the DMEC in strict confidence, at 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 Spoke CTUs in California and Singapore. 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 CTUs (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.

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 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 CTUs in the case of non-UK sites). In addition, the CTRU will hold electronic information on all trial patients. All Spoke CTUs will have controlled access to the trial database. Each 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 Spoke CTUs 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 number.
- 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 relevant Spoke CTU. However, all other data collection forms that are transferred to or from the CTRU or other Spoke CTUs will be coded with a 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 Spoke CTUs 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.

16 Statement of Indemnity

This trial is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm 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 clinical negligence and other negligent harm to UK patients 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.

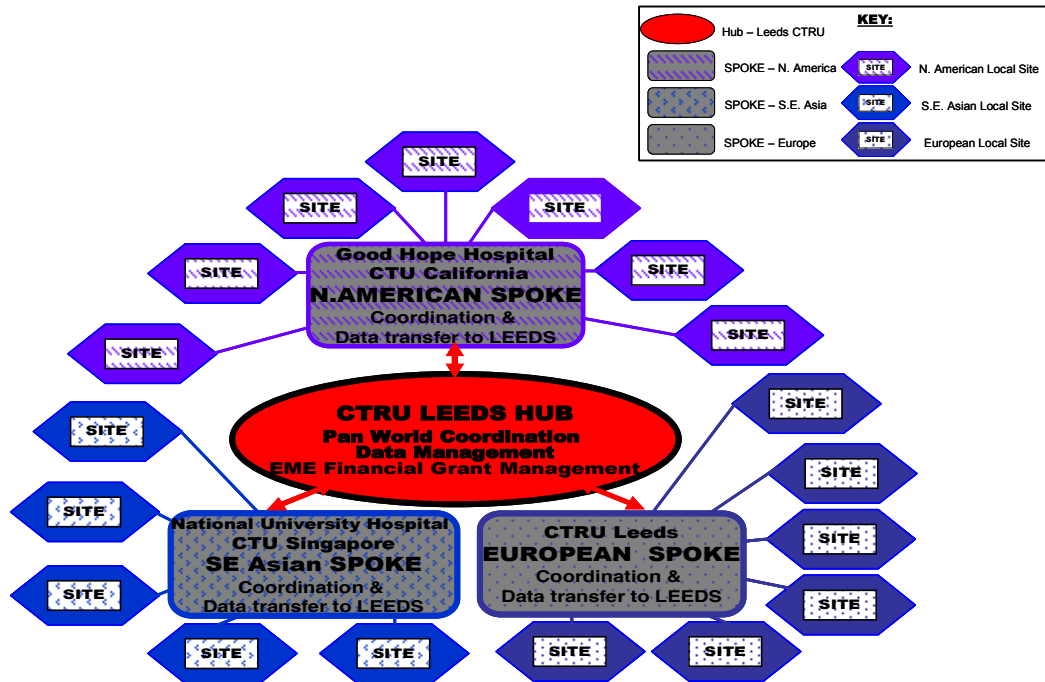
As this is a clinician-led trial there are no arrangements for no-fault compensation.

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 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 regional Spoke CTU for advice and support on trial set-up and operation, and submission of trial data. In turn, Spoke CTUs 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.

International Spoke CTUs will have delegated responsibility for the conduct of the trial within their unit and affiliated 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 Leads, 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 CTUs.

International Spoke CTU: the Spoke CTUs 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

This trial is funded by the Medical Research Council (MRC) Efficacy & Mechanism Evaluation (EME) programme which is 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) Guidelines [31], 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 [32]:

- 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 Leads, other ROLARR grant applicants, and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators 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 ten recruiting Principal Investigators 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.

19 References

1. Clinical Outcomes of Surgical Therapy Study Group. *N Eng J Med*; 2004;350(20):2050-9,
2. Tang,C.L et al. *Br J Surg*.2001; 88(6):801-7,
3. Jayne D.G et al. *J Clin Oncol*; 2007;25(21):3061-8
4. Guillou PJ et al. *The Lancet* 2005; 365:1718-26.
5. Jayne DG et al. *J Clin Oncol* 2007; 25: 3061-8.
6. Taylor GW et al. *IJMRCAS* 2007; 3: 3-9.
7. Smith A et al. *Surgery* 2006; 24:74-8
8. Jayne DG et al. *Br J Surg*. 2005; 92: 1124-32.
9. DeNoto G et al. *J Lap Adv Surg tech* 2006; 16: 551-6.
- 10.Hildebrandt U et al. *Dis Colon Rectum* 2003;46:1640-5.
- 11.Pigazzi A et al. *Surg Endosc* 2006; 10: 1521-5.
- 12.Baik SH et al *Surg Endoscopy* 2008; 22:1601-8.
- 13.D'Annibale A et al. *Dis Colon Rectum* 2004;47: 2162-8.
- 14.Rawlings AL et al. *Surg Endosc* 2006;11:1713-8.
- 15.Rawlings AL et al. *Surg Endosc* 2007; 21:1701-8.
- 16.Hellan M et al. *Ann Surg Oncol* 2007; 14: 3168-73.
- 17.Mirnezami AH et al. *Colorectal Dis. Accepted Article*"; doi: 10.1111/j.1463-1318.2009.01999.x
- 18.The Royal College of Pathologists: Dataset for colorectal cancer (2nd edition) Sept 2007
www.rcpath.org/resources/pdf/G049-ColorectalDataset-Sep07
- 19.Vassiliou MC et al. *Am J Surg*. 2005;190:107-13.
- 20.Barry MJ et al. *J Urol*. 1992;148:1549-57
- 21.Rosen RC et al. *Urology* 1997;49:822-30.
- 22.Rosen R et al. *J Sex Marital Ther* 2002;26:191-208.
- 23.E. M. Smets et al. *Br J Cancer*. 1996 January; 73(2): 241–245.
- 24.Dolan P. 1997, *Medical Care*; 335:1095-1108.
- 25.Punt CJA et al. *J Natl Cancer Inst* 2007;99:998-1003.
- 26.Aziz O et al *Ann Surg Oncol* 2006;13:413-24.
- 27.Moloo H et al. *Surg Endoscopy* 2004;18:732-5.
- 28.Wood J et al. *J Health Serv Res Policy* 1999; 4: 226-9.
- 29.Laparoscopic surgery for colorectal cancer. NICE technology appraisal no. 105 (2006).
www.nice.org.uk/TA105
- 30.Ramsay CR et al. *Health Technology Assessment* 2001; 5:1-79.
- 31.De Angelis C et al. *CMAJ* 2004;171(6):606-7.
- 32.http://www.icmje.org/ethical_1author.html
- 33.Shepherd et al. *J Clin Pathol*.1995 ; 48: 849-55

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 TNM6 due to the poor reproducibility of the TNM6 definitions of extramural vascular invasion and lymph nodes. This therefore means that the 3mm rule will be used for nodal involvement. This also allows this study to be consistent with other trials such as the Dutch TME trial, CR07 etc.

In a recent study the CRM has been shown to be involved in 31% of abdomino-perineal resections (APRs) compared to 12% of anterior resections (ARs). This was also seen in the MRC CLASICC study where 21% of APRs showed margin involvement vs 10% of ARs. In the Mercury study, 33% of APRs vs 13% of ARs below 6cm showed CRM positivity, in the Dutch TME/RT study 29% of APRs had margin involvement vs 13% of ARs and in the Norwegian national audit of curative excisions of rectal cancer 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) and in the Norwegian study (16% APRs vs 4% ARs). 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 front, back 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 of the tumour or mucosa and the place of the perforation. 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 2-5cms 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 distance of involvement. 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 fifteen is to be expected in cases not undergoing preoperative neo-adjuvant therapy.

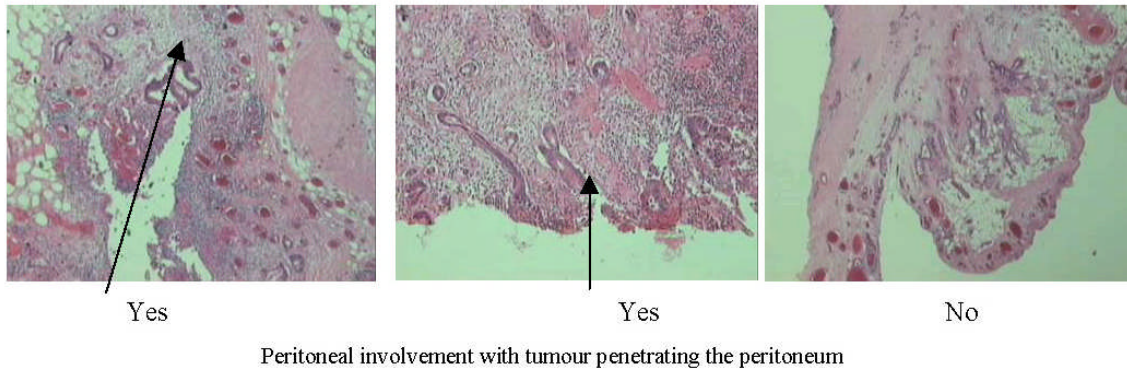
Involvement of the peritoneum is defined as per Shepherd et al [33] and extramural vascular invasion when involvement of a vascular structure with smooth muscle in the wall is apparent. This should be looked for closely and if tumour is present close to an arterial structure without an accompanying vein have a high level of suspicion. Involvement of the CRM is defined as tumour within 1 mm of the CRM.

The digital photographs (front, back and slices) should be sent to the CTRU along with the histopathology CRF.

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 there is a proposal to call both internal and external sphincter involvement T4. 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 should be assessed by the method of Shepherd et al [33].



A

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.

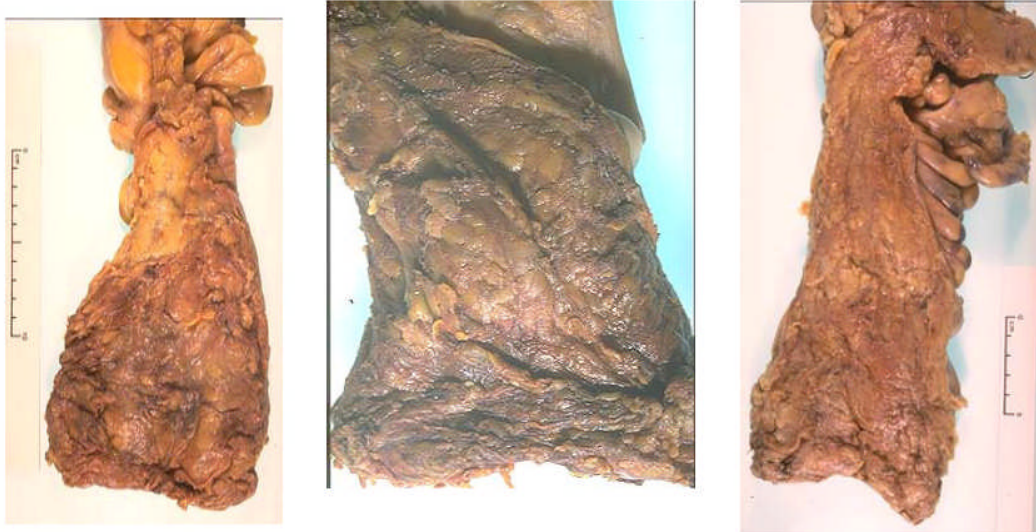
20.3.2 Quality of resection of the mesorectum

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 $> 1 \text{ cm}^2$ or incision down to muscularis propria.

Irregular CRM with little bulk and little clearance anteriorly

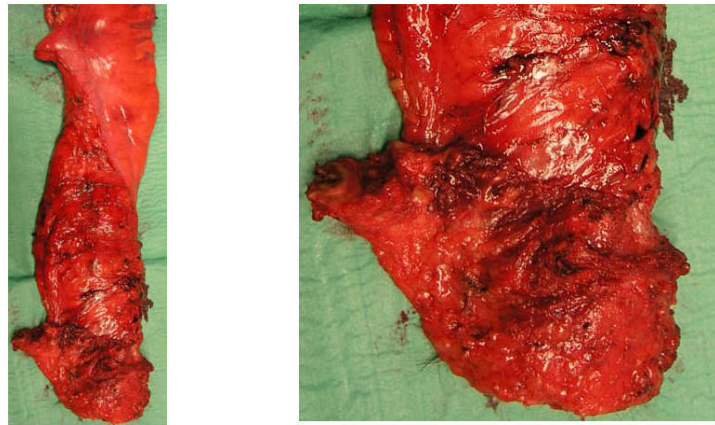
20.3.3 Quality of resection (abdomino-perineal resection only)

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

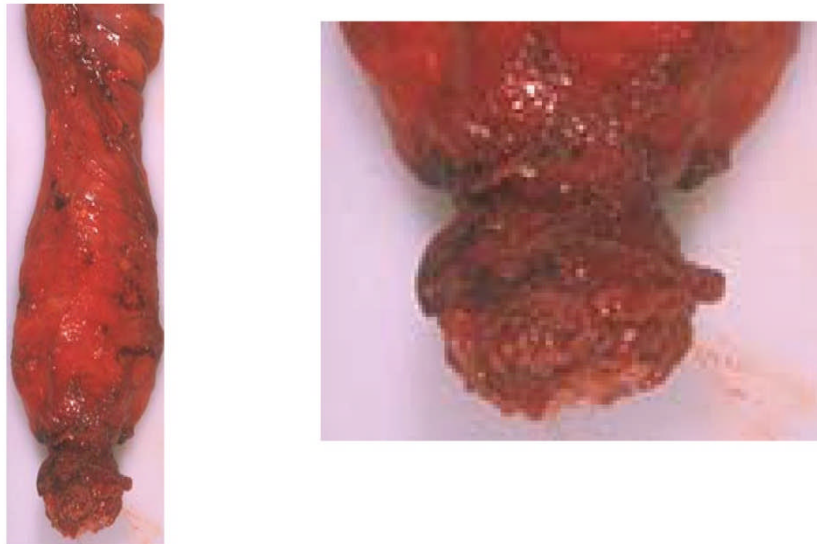
Levator plane

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.

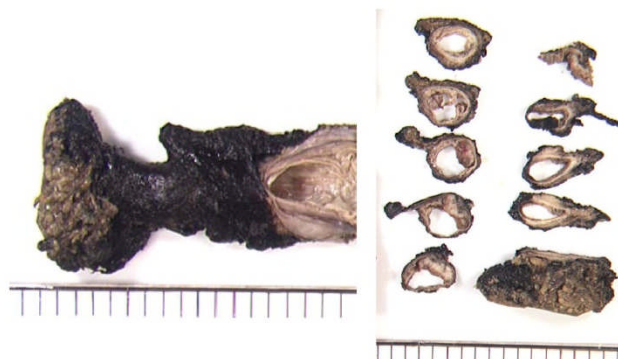
Levator plane



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.

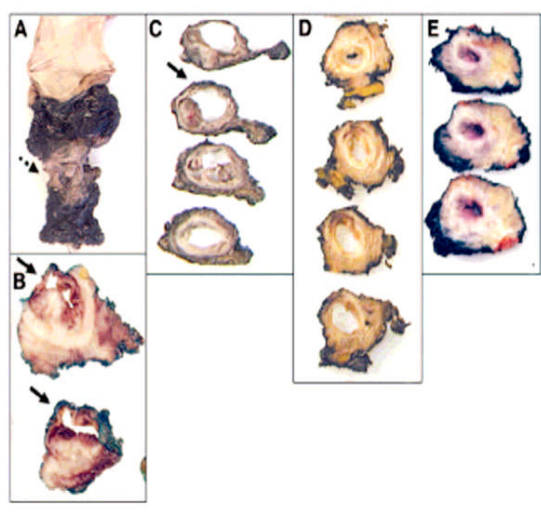


Intrasphincteric/submucosal plane: The surgeon has inadvertently entered the sphincters or even deeper into the submucosa or perforated the specimen at any point.



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 /submucosa D: 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

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 5 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

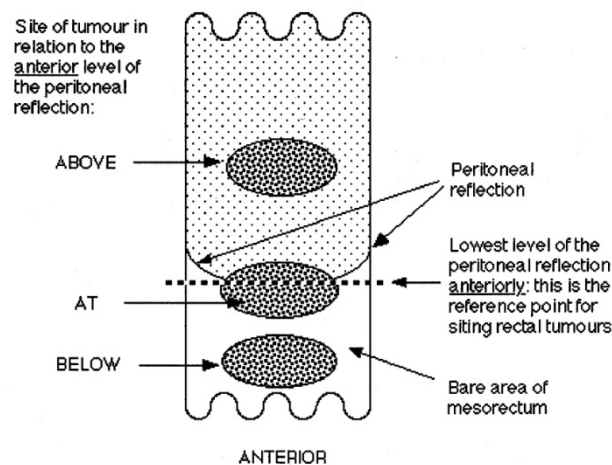
combinations of the above. However, to correlate the position with the MRI report the tumour should be reported from the distal resection margin with the mesorectum posterior and the peritoneal reflection anterior. This can be documented as a relationship to a clock-face on the reporting proforma.

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.

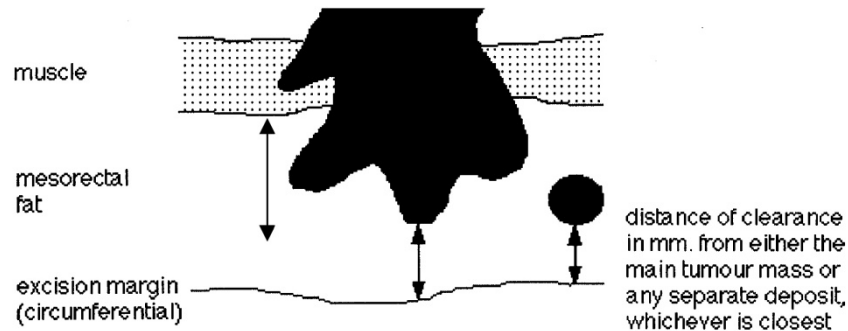
It is recommended that the whole of this margin (i.e. the mesorectum) be painted with a marker such as silver nitrate or India Ink before dissecting the specimen. The tumour is then best sliced serially at 3-4 mm intervals to select blocks from the area above and below the tumour to look for metastatic 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 30mm 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, undifferentiated and high-grade dysplasia should be documented.

21 Appendix 2: Global rating scale component of the intraoperative assessment tool (GOALS)* [19]

Depth perception

1. Constantly overshoots target, wide swings, slow to correct
- 2.
3. Some overshooting or missing of target, but quick to correct
- 4.
5. Accurately directs instruments in the correct plane to target

Bimanual dexterity

1. Uses only one hand, ignores non-dominant hand, poor coordination between hands
- 2.
3. Uses both hands, but does not optimize interaction between hands
- 4.
5. Expertly uses both hands in a complimentary manner to provide optimal exposure

Efficiency

1. Uncertain, inefficient efforts; many tentative movements; constantly changing focus or persisting without progress
- 2.
3. Slow, but planned movements are reasonably organized
- 4.
5. Confident, efficient and safe conduct, maintains focus on task until it is better performed by way of an alternative approach

Tissue handling

1. Rough movements, tears tissue, injures adjacent structures, poor grasper control, grasper frequently slips
- 2.
3. Handles tissues reasonably well, minor trauma to adjacent tissue (i.e. occasional unnecessary bleeding or slipping of the grasper)
- 4.
5. Handles tissues well, applies appropriate traction, negligible injury to adjacent structures

Autonomy

1. Unable to complete entire task, even with verbal guidance
- 2.
3. Able to complete task safely with moderate guidance
- 4.
5. Able to complete task independently without prompting

** The descriptors shown are the “anchor” descriptors for scores 1, 3, and 5.*

22 Abbreviations Used

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

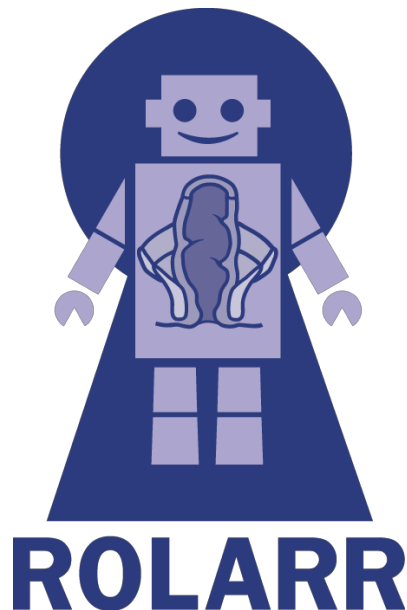


Clinical Trials Research Unit (CTRU)

University of Leeds

Leeds LS2 9JT

<http://ctr.u.leeds.ac.uk>



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

**Chief Investigator
and Hub Lead:**

Professor David Jayne
Professor of Surgery
Section of Translational Anaesthesia and Surgery
Leeds Institute of Biological and Clinical Sciences
Level 7 Clinical Sciences Building
St James's University Hospital
Leeds LS9 7TF, UK

North American Spoke Lead:

Professor Alessio Pigazzi
Associate Professor of Surgery
University of California, Irvine
California, USA

This project was awarded by the Efficacy and Mechanism Evaluation (EME) programme*, and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership.

Project Reference: 08/52/01

The Sponsor and CTRU accept no responsibility for the accuracy of additional documentation or instructions developed by collaborating or third party organisations from the content of this protocol.

*The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D Division, Public Health Agency in Northern Ireland. It is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) based at the University of Southampton.

Key Contacts

Chief Investigator:

Professor David Jayne
Professor of Surgery
Leeds Institute of Clinical & Biological
University of Leeds

Tel: +44 113 206 5218
Fax: +44 113 244 9168
Email: djayne@leeds.ac.uk

Queries for the CTRU:

ROLARR@leeds.ac.uk

Trial Management:

Miss Julie Croft
Senior Trial Manager
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds

Tel: +44 113 343 8394
Fax: +44 113 343 1471
Email: j.croft@leeds.ac.uk

Miss Alexandra Smith
Head of Trial Management - Solid Tumours
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds

Tel: +44 113 343 2657
Fax: +44 113 343 1471
Email: a.f.smith@leeds.ac.uk

Dr Fiona Collinson
Senior Lecturer (Oncology and Clinical Trials)
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds

Tel: +44 113 343 1491
Fax: +44 113 343 1471
Email: f.j.collinson@leeds.ac.uk

Statistics:

Mrs Helen Marshall
Principal Statistician
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds

Tel: +44 113 343 1481
Fax: +44 113 343 1471
Email: h.c.marshall@leeds.ac.uk

Mr Neil Corrigan
Medical Statistician
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds

Tel: +44 113 343 8016
Fax: +44 113 343 1471
Email: n.corrigan@leeds.ac.uk

Professor Julia Brown
Director of Clinical Trials Research Unit
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds

Tel: +44 113 343 1477
Fax: +44 113 343 1471
Email: j.m.b.brown@leeds.ac.uk

Health Economics:

Professor Claire Hulme
Professor of Health Economics
Academic Unit of Health Economics
University of Leeds

Tel: +44 113 343 6989
Fax: +44 113 343 3470
Email: c.t.hulme@leeds.ac.uk

Dr Richard Edlin
Visiting Senior Lecturer in Health Economics
Academic Unit of Health Economics
University of Leeds

Tel: +44 113 343 0879
Fax: +44 113 343 3470
Email: r.p.edlin@leeds.ac.uk

Pathology:

Professor Phil Quirke
Professor of Pathology
Pathology, Anatomy and Tumour Biology

Tel: +44 113 343 8407
Fax: +44 113 343 8431



Protocol Version 6.0, 01 July 2015

ISRCTN: 80500123

REC Reference: 10/H1307/27

Institute of Cancer and Pathology
University of Leeds

Email: p.quirke@leeds.ac.uk

US Clinical Lead:

Professor Alessio Pigazzi
Associate Professor of Surgery
University of California, Irvine
California, USA

Tel: +1 714 456 5443

Fax: +1 714 456 6027

Email: apigazzi@uci.edu

Patient Advisor:

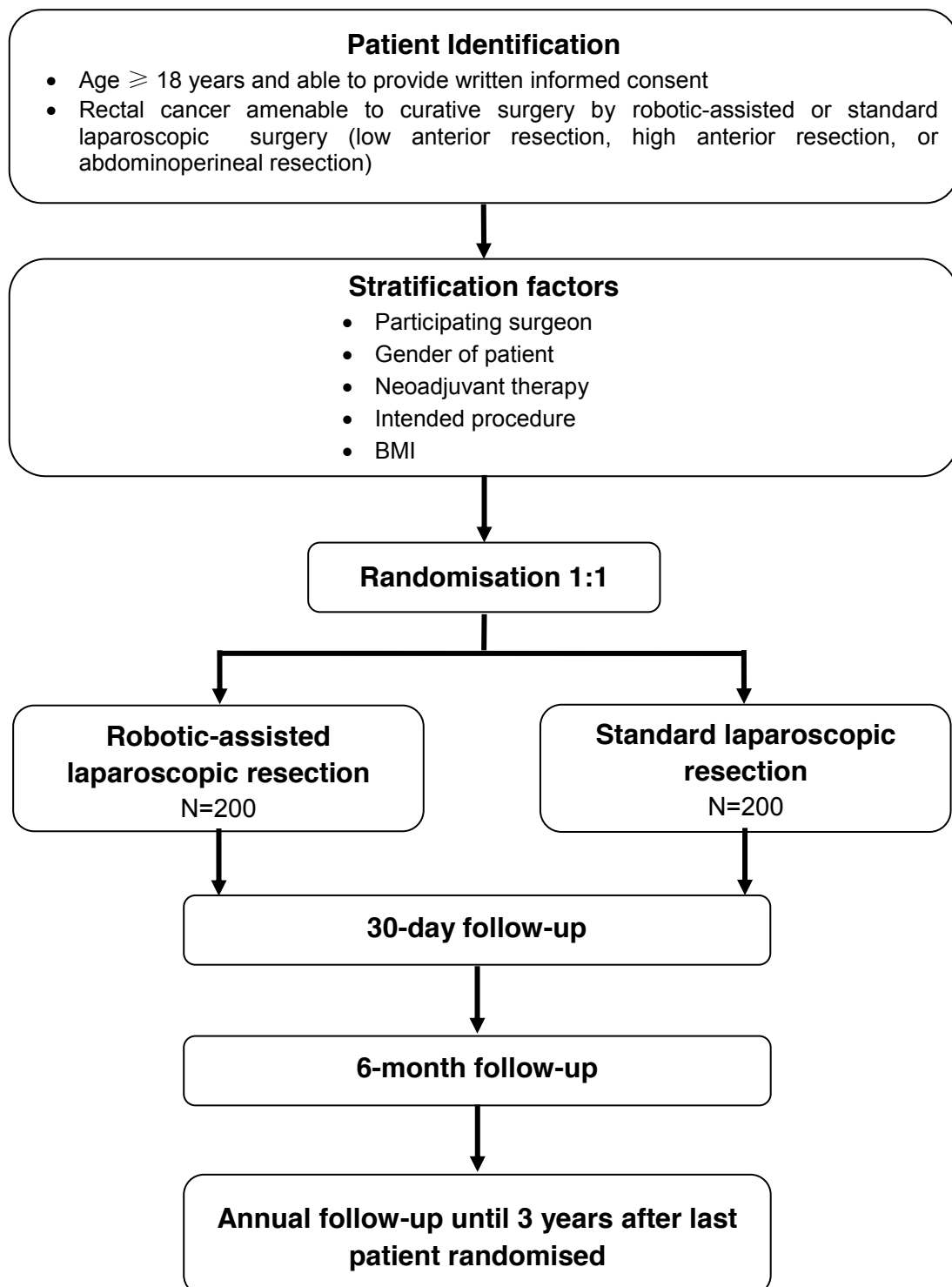
Mr Christopher Garbett

Contents

1	TRIAL SUMMARY	3
2	BACKGROUND	4
2.1	EXISTING RESEARCH	4
2.2	RISKS AND BENEFITS.....	5
2.3	RATIONALE FOR CURRENT STUDY	6
2.4	AIMS AND OBJECTIVES	6
3	DESIGN.....	7
4	ELIGIBILITY.....	7
4.1	PATIENT ELIGIBILITY	7
4.2	SITE ELIGIBILITY.....	8
4.3	SURGEON ELIGIBILITY	9
5	RECRUITMENT AND RANDOMISATION OF PATIENTS.....	9
5.1	RECRUITMENT OF PATIENTS	9
5.2	RANDOMISATION	10
5.3	NON-RANDOMISATION.....	11
6	INTERVENTION DETAILS	11
6.1	PRE-OPERATIVE INVESTIGATION AND PREPARATION.....	11
6.2	SURGERY	12
6.3	POST-OPERATIVE CARE	12
6.4	WITHDRAWAL OF TREATMENT	12
7	ASSESSMENT AND DATA COLLECTION	12
7.1	SUBMISSION OF TRIAL DATA.....	13
7.2	SCHEDULE OF EVENTS	13
7.3	PRE-OPERATIVE ASSESSMENTS AND DATA COLLECTION.....	16
7.4	OPERATIVE ASSESSMENTS AND DATA COLLECTION.....	16
7.5	PATHOLOGY ASSESSMENT	16
7.6	POST-OPERATIVE ASSESSMENT AND DATA COLLECTION	18
7.7	FOLLOW-UP ASSESSMENT AND DATA COLLECTION.....	18
7.8	DEATH	19
7.9	PREGNANCY	19
7.10	QUALITY OF LIFE AND HEALTH ECONOMIC ASSESSMENT.....	19
7.11	DEFINITION OF END OF STUDY	19
8	SAFETY REPORTING.....	19
8.1	GENERAL DEFINITIONS	20
8.2	ROLARR EXPECTED COMPLICATIONS	21
8.3	REPORTING OF COMPLICATIONS.....	21
8.4	DEATHS.....	23
8.5	SERIOUS BREACHES OF GOOD CLINICAL PRACTICE (GCP).....	23
8.6	RESPONSIBILITIES FOR SAFETY REPORTING.....	23
8.7	REPORTING	24
9	QUALITY OF LIFE.....	24

10	ECONOMIC EVALUATION	25
11	ENDPOINTS	26
11.1	PRIMARY ENDPOINT.....	26
11.2	SECONDARY ENDPOINTS	26
12	STATISTICAL CONSIDERATIONS	27
12.1	SAMPLE SIZE	27
13	STATISTICAL ANALYSIS	29
14	DATA MONITORING	32
14.1	DATA MONITORING AND ETHICS COMMITTEE.....	32
14.2	DATA MONITORING	32
14.3	CLINICAL GOVERNANCE ISSUES.....	33
15	QUALITY ASSURANCE, ETHICAL CONSIDERATIONS, AND CONFIDENTIALITY	33
15.1	QUALITY ASSURANCE	33
15.2	ETHICAL CONSIDERATIONS.....	33
15.3	CONFIDENTIALITY	34
15.4	ARCHIVING.....	34
16	STATEMENT OF INDEMNITY	35
17	STUDY ORGANISATIONAL STRUCTURE	35
17.1	RESPONSIBILITIES.....	36
17.2	OPERATIONAL STRUCTURE	37
17.3	FUNDING	38
18	PUBLICATION POLICY	38
19	REFERENCES	39
20	APPENDIX 1: PATHOLOGICAL REPORTING	41
20.1	PREPARATION OF THE SPECIMEN.....	41
20.2	DISSECTION	42
20.3	T STAGING OF LOW RECTAL CANCERS	42
20.4	CHEMORADIOTHERAPY RESPONSE SCORING	46
20.5	ASSESSMENT OF SPECIMENS WHERE TUMOUR CELLS ARE DIFFICULT TO FIND	46
20.6	DEFINITIONS USED IN PATHOLOGY	47
21	APPENDIX 2: ASA PHYSICAL STATUS CLASSIFICATION SYSTEM[38]	49
22	APPENDIX 3: ABBREVIATIONS USED	50
23	APPENDIX 4: Low Anterior Resection Syndrome (LARS) Supplementary Study	51

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 criteria¹

1. Aged ≥ 18 years
2. Able to provide written informed consent
3. Diagnosis of rectal cancer² amenable to curative surgery³ 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. Pregnancy⁴
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:

- Site able to perform both robotic-assisted and standard laparoscopic rectal cancer surgery
- Established expertise in clinical trial involvement as determined from sites' feasibility questionnaire
- 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)
- BMI⁵ (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 (\pm 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 \pm 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 \leq 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 diagnosis⁶
- 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 intrasphincteric/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 (\pm 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 diagnosis⁷
- 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-threatening⁸
- 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/compartament 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 ≤ 1 mm 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 recurrence⁹. 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 cancer⁷.
- 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 ≤ 1 mm 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 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. 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.

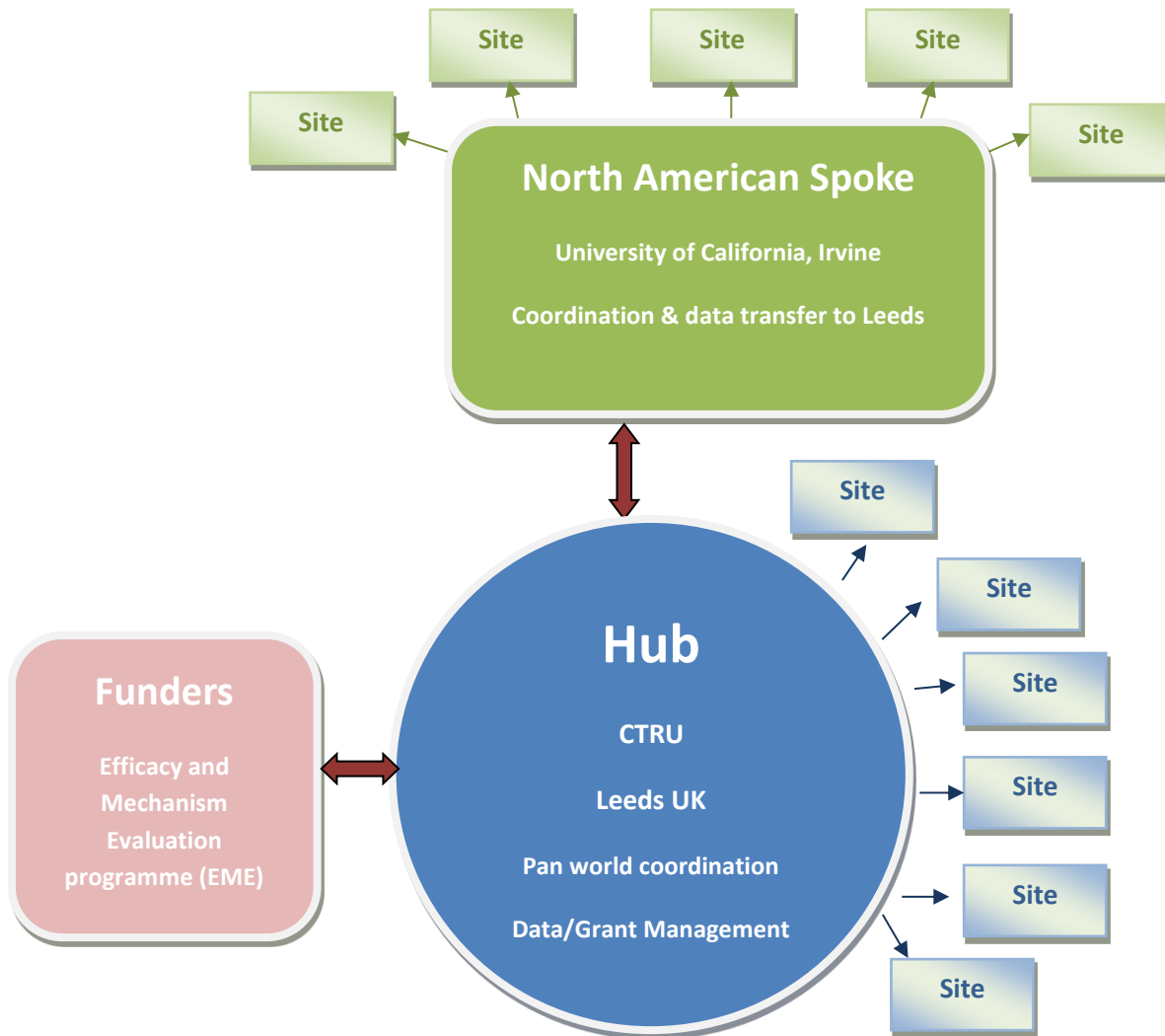
Research sites outside of the UK will be liable for clinical negligence and other negligent harm to patients under their care whether or not this arises as a result of trial-specific procedures.

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.

19 References

1. Jayne, D.G., et al., *Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group*. J Clin Oncol, 2007. **25**(21): p. 3061-8.
2. *A comparison of laparoscopically assisted and open colectomy for colon cancer*. N Engl J Med, 2004. **350**(20): p. 2050-9.
3. Tang, C.L., et al., *Randomized clinical trial of the effect of open versus laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer*. Br J Surg, 2001. **88**(6): p. 801-7.
4. Guillou, P.J., et al., *Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial*. Lancet, 2005. **365**(9472): p. 1718-26.
5. Jayne, D. G., Thorpe, H. C., Copeland, J., Quirke, P., Brown, J. M., Guillou, P. J. *Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer*. Br J Surg, 2010. **97**(11): 1638-45.
6. Smith, A., J. Smith, and D.G. Jayne, *Telerobotics: surgery for the 21st century*. Surgery (Oxford), 2006. **24**(2): p. 74-78.
7. Taylor, G.W., *Minimally Invasive Robotic Association 2nd international congress: the Union League Club, New York, NY, USA, 18-20 January 2007*. Int J Med Robot, 2007. **3**(3): p. 281-6.
8. Jayne, D.G., et al., *Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique*. Br J Surg, 2005. **92**(9): p. 1124-32.
9. Hildebrandt, U., et al., *Single-surgeon surgery in laparoscopic colonic resection*. Dis Colon Rectum, 2003. **46**(12): p. 1640-5.
10. DeNoto, G., E. Rubach, and T.S. Ravikumar, *A standardized technique for robotically performed sigmoid colectomy*. J Laparoendosc Adv Surg Tech A, 2006. **16**(6): p. 551-6.
11. Baik, S.H., et al., *Robotic tumor-specific mesorectal excision of rectal cancer: short-term outcome of a pilot randomized trial*. Surg Endosc, 2008. **22**(7): p. 1601-8.
12. Pigazzi, A., et al., *Robotic-assisted laparoscopic low anterior resection with total mesorectal excision for rectal cancer*. Surg Endosc, 2006. **20**(10): p. 1521-5.
13. D'Annibale, A., et al., *Robotic and laparoscopic surgery for treatment of colorectal diseases*. Dis Colon Rectum, 2004. **47**(12): p. 2162-8.
14. Rawlings, A.L., J.H. Woodland, and D.L. Crawford, *Telerobotic surgery for right and sigmoid colectomies: 30 consecutive cases*. Surg Endosc, 2006. **20**(11): p. 1713-8.
15. Rawlings, A.L., et al., *Robotic versus laparoscopic colectomy*. Surg Endosc, 2007. **21**(10): p. 1701-8.
16. Hellan, M., et al., *Short-term outcomes after robotic-assisted total mesorectal excision for rectal cancer*. Ann Surg Oncol, 2007. **14**(11): p. 3168-73.
17. Mirnezami, A.H., et al., *Robotic colorectal surgery: hype or new hope? A systematic review of robotics in colorectal surgery*. Colorectal Dis, 2009.
18. Barry, M.J., et al., *The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association*. J Urol, 1992. **148**(5): p. 1549-57; discussion 1564.
19. Rosen, R.C., et al., *The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction*. Urology, 1997. **49**(6): p. 822-30.

20. Rosen, R., et al., *The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function*. J Sex Marital Ther, 2000. **26**(2): p. 191-208.
21. Smets, E.M., et al., *Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy*. Br J Cancer, 1996. **73**(2): p. 241-5.
22. The Royal College of Pathologists. *Dataset for colorectal cancer*. 2007; 2nd:[Available from: <http://www.rcpath.org/resources/pdf/G049-ColorectalDataset-Sep07.pdf>].
23. Sobin, L.H. and I.D. Fleming, *TNM Classification of Malignant Tumors, fifth edition (1997)*. Union Internationale Contre le Cancer and the American Joint Committee on Cancer. Cancer, 1997. **80**(9): p. 1803-4.
24. *AJCC Cancer Staging Manual*. 5th ed, ed. I.D. Fleming, et al. 1997, Philadelphia, PA: Lippincott-Raven.
25. Dolan, P., *Modeling valuations for EuroQol health states*. Med Care, 1997. **35**(11): p. 1095-108.
26. Punt, C.J., et al., *Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials*. J Natl Cancer Inst, 2007. **99**(13): p. 998-1003.
27. Aziz, O., et al., *Laparoscopic versus open surgery for rectal cancer: a meta-analysis*. Ann Surg Oncol, 2006. **13**(3): p. 413-24.
28. Moloo, H., et al., *Laparoscopic resections for colorectal cancer: does conversion survival?* Surg Endosc, 2004. **18**(5): p. 732-5.
29. Wood, J. and M. Lambert, *Sample size calculations for trials in health services research*. J Health Serv Res Policy, 1999. **4**(4): p. 226-9.
30. NICE (2006) *Laparoscopic surgery for colorectal cancer (review)*. NICE technology appraisal guidance **105**.
31. Ramsay, C.R., et al., *Statistical assessment of the learning curves of health technologies*. Health Technol Assess, 2001. **5**(12): p. 1-79.
32. De Angelis, C., et al., *Clinical trial registration: a statement from the International Committee of Medical Journal Editors*. CMAJ, 2004. **171**(6): p. 606-7.
33. Shihab, O.C., et al., *Patients with low rectal cancer treated by abdominoperineal excision have worse tumors and higher involved margin rates compared with patients treated by anterior resection*. Dis Colon Rectum, 2010. **53**(1): p. 53-6.
34. Nagtegaal, I.D., et al., *Low rectal cancer: a call for a change of approach in abdominoperineal resection*. J Clin Oncol, 2005. **23**(36): p. 9257-64.
35. Wibe, A., et al., *Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection*. Dis Colon Rectum, 2004. **47**(1): p. 48-58.
36. Shepherd, N.A., K.J. Baxter, and S.B. Love, *Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer*. J Clin Pathol, 1995. **48**(9): p. 849-55.
37. Dworak, O., L. Keilholz, and A. Hoffmann, *Pathological features of rectal cancer after preoperative radiochemotherapy*. Int J Colorectal Dis, 1997. **12**(1): p. 19-23.
38. ASA Physical Status Classification System accessed 29/06/2010. <http://www.asahq.org/clinical/physicalstatus.htm>.

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.

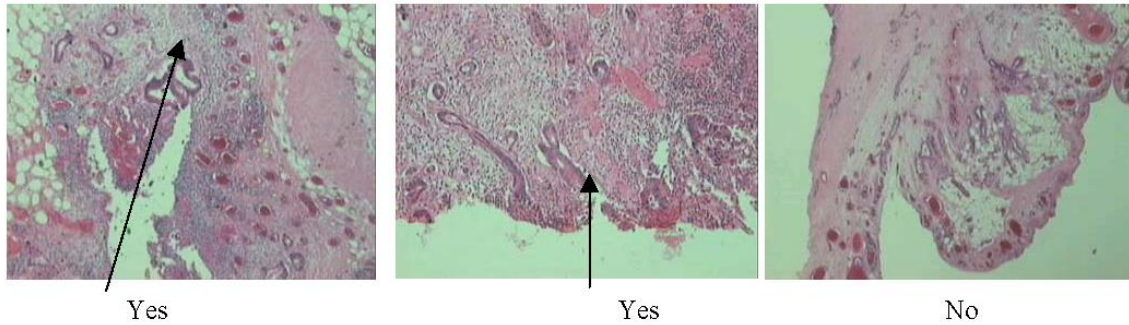
Involvement of the peritoneum is defined as per Shepherd et al[36] and extramural vascular invasion when involvement of a vascular structure with smooth muscle in the wall is apparent. This should be looked for closely and if tumour is present close to an arterial structure without an accompanying vein 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.

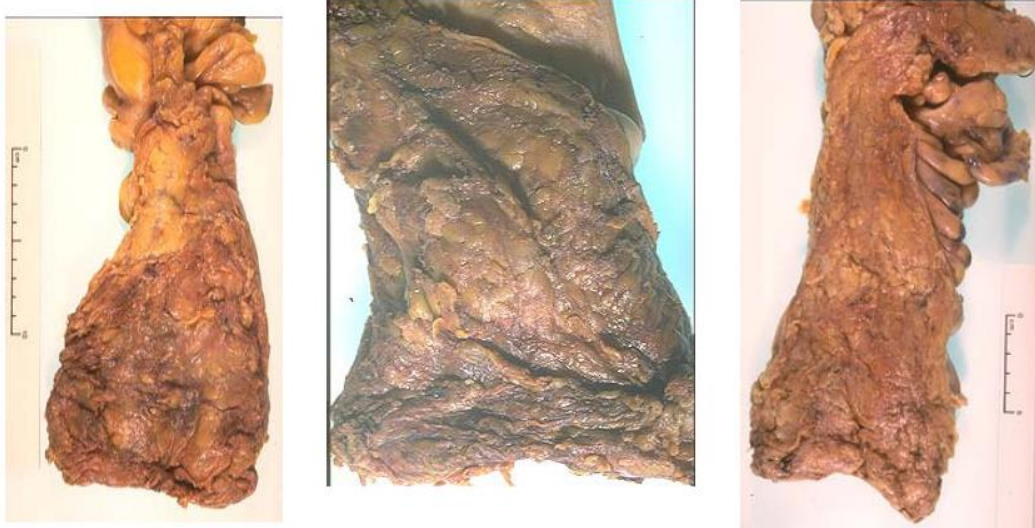
20.3.2 Quality of resection of the mesorectum

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 cm² or incision down to muscularis propria.

Irregular CRM with little bulk and little clearance anteriorly

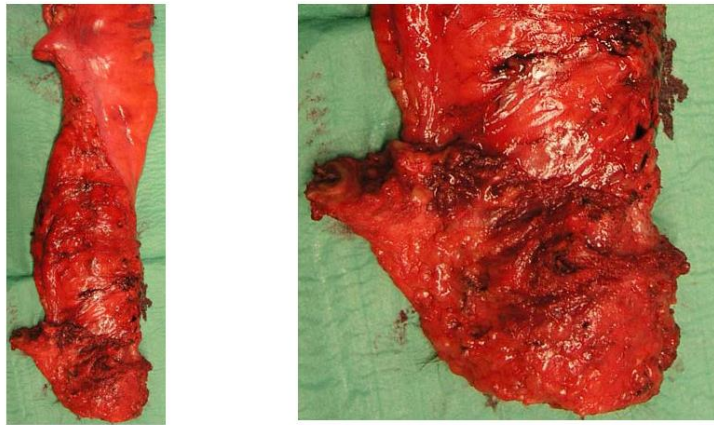
20.3.3 Quality of resection (abdomino-perineal resection only)

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.

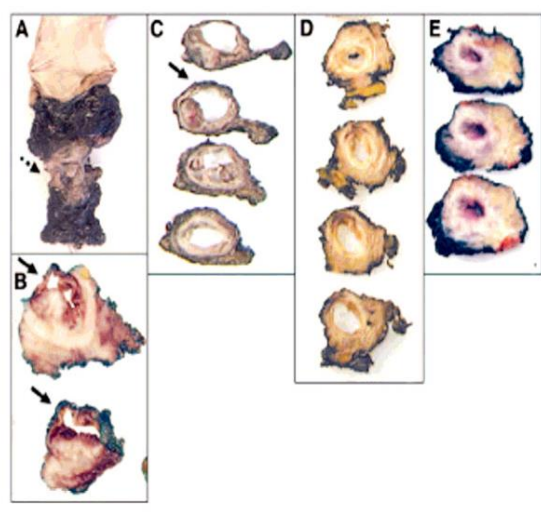


Intrasphincteric/submucosal/perforation plane: The surgeon has inadvertently entered the sphincters or even deeper into the submucosa or perforated the specimen at any point.



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 /submucosa D: 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

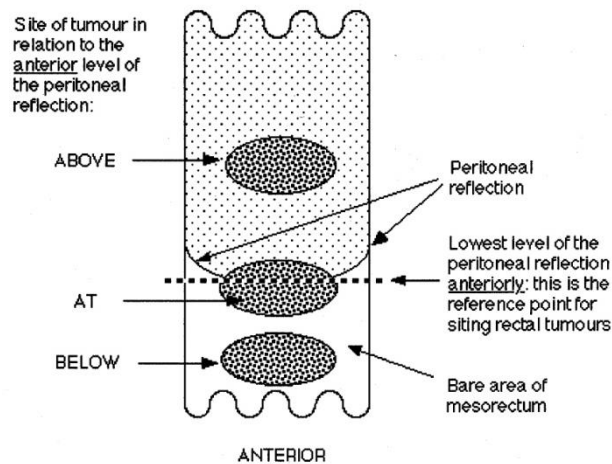
The position of the tumour should be accurately noted. Initially this involves documentation of the surface involvement – i.e. anterior quadrant, posterior quadrant, lateral quadrant and combinations of the above. However, to correlate the position with the MRI report the tumour should be reported from 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.

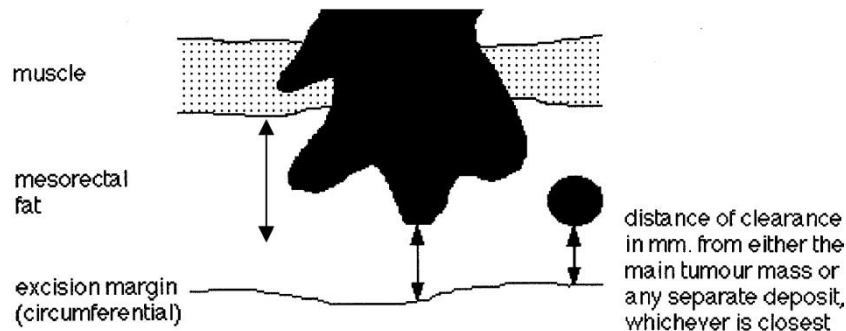
It is recommended that the whole of this margin (i.e. the mesorectum) be painted with a marker such as silver nitrate or India Ink before dissecting the specimen. The tumour is then best sliced serially at 3-4 mm intervals to select blocks from the area above and below the tumour to look for metastatic 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	MFI-20	Multi-dimensional Fatigue Inventory-20
AR	Anterior resection	MRC	Medical Research Council
ASA	American Society of Anaesthetists	MRI	Magnetic resonance imaging
BMI	Body Mass Index	NHS	National Health Service (UK)
CI	Chief Investigator	NIHR	National Institute for Health Research (UK)
CRF	Case report form	NRES	National Research Ethics Service (UK)
CRM	Circumferential resection margin	PI	Principal Investigator
CTRU	Clinical Trials Research Unit	PPI	Patient and public involvement
CTU	Clinical Trials Unit	PRO	Patient reported outcomes
DMEC	Data Monitoring and Ethics Committee	PSSRU	Personal Social Services Research Unit
DVT	Deep vein thrombosis	QALY	Quality Adjusted Life Year
EME	Efficacy and Mechanisms Evaluation	QoL	Quality of Life
EQ-5D	EuroQol-5 Dimensions	REC	Research Ethics Committee
FSFI	Female Sexual Function Index	SDV	Source data verification
GCP	Good Clinical Practice	SF-36v2	Short-Form 36 version 2
ICER	Incremental cost-effectiveness ratio	SOP	Standard operating procedure
IIEF	International Index of Erectile Function	SSA	Site Specific Assessment (UK)
IMA	Inferior mesenteric artery	TME	Total mesorectal excision
IMV	Inferior mesenteric vein	TMG	Trial Management Group
I-PSS	International Prostatic Symptom Score	TSC	Trial Steering Committee
ISF	Investigator site file	USC	Unexpected Serious Complication
ITT	Intention to treat		

23 Appendix 4: Low Anterior Resection Syndrome (LARS) Supplementary Study

Introduction

Colorectal cancer is common in Europe, with at least one third of all colorectal cancers arising from the rectum (1). Surgery for rectal cancer involves resection of the primary cancer with either restoration of gastrointestinal continuity or formation of a permanent stoma. Restoration of gastrointestinal continuity (anterior resection) involves surgically joining the proximal colon to the rectal remnant as an anastomosis, which may be defunctioned by a temporary stoma that is reversed once anastomotic healing has occurred. Creation of a permanent stoma (Abdominoperineal resection or Hartmann's procedure) is undertaken when the cancer is too close to or involving the anal sphincters, or when the formation of a primary anastomosis is unsafe due to technical considerations or patient co-morbidity. The standard approach to rectal cancer surgery has been to restore gastrointestinal continuity (sphincter-sparing surgery) wherever possible and safe to do so. However, loss of the normal rectal reservoir function can result in severe defaecatory dysfunction, which is more pronounced as the level of the anastomosis approaches the anal sphincter complex. The resulting syndrome, low anterior resection syndrome (LARS), can severely impact on quality of life, causing symptoms due to faecal urgency, incontinence, obstructive defecation, fragmentation and stool clustering. LARS is estimated to affect between 50% - 90% of patients undergoing low anterior resection (2-3). It is a difficult condition to treat, with some 5% of patients ultimately requiring a permanent stoma (4). A policy of restoring gastrointestinal continuity wherever technically possible, and particularly in low rectal cancers, is therefore questionable in terms of long-term patient QoL. This has been reinforced by a recent Cochrane meta-analysis that reported little difference in QoL following rectal cancer surgery between patients with and without a stoma (5).

Until recently, research into LARS was restricted by the lack of a standardised scoring system. In 2012, Emmertson et al described the LARS score (6) and later validated it across six languages (English, Swedish, Spanish, German, Danish and Chinese) (7-9). The LARS score is a simple, five-item, self-administered questionnaire measuring bowel dysfunction after rectal cancer surgery. An opportunity exists to apply the validated LARS score to the ROLARR study. This will enable, for the first time, accurate data to be captured on the incidence, severity, aetiology, treatment, and outcomes for patients suffering LARS after elective rectal cancer surgery with curative intent.

Objectives

To explore the incidence, severity, aetiology, treatment, and outcomes for patients suffering low anterior resection syndrome (LARS) following elective rectal cancer surgery as part of the ROLARR trial.

Study Design

A retrospective cohort study involving postal survey of patient reported outcomes. The study will also utilise data collected during the main ROLARR trial

Patient Population

Eligible ROLARR participants from Denmark, Germany, Italy, United Kingdom and United States of America will be invited to complete a one-off postal survey.

Design

Participating sites will assess participant eligibility of ROLARR participants using the inclusion and exclusion criteria for this supplementary study. Eligible ROLARR participants will then be sent a participant information sheet and questionnaire via postal mail directly from the site.

Participation in the LARS study is entirely voluntary. A pre-paid return envelope will be provided and consent to participate will be implied upon successful receipt of the completed questionnaire at the Spoke Clinical Trials Unit

Inclusion criteria

- Patients enrolled in ROLARR with intact gastrointestinal tract
- Patients alive and free of local/pelvic disease recurrence (distant, non-pelvic disease recurrence is permissible)
- Patients enrolled in the ROLARR study from the following countries: Denmark, Germany, Italy, United Kingdom and United States of America).

Exclusion Criteria:

- Patients with a current stoma (permanent or unreversed temporary stoma)
- Known or suspected local/pelvic disease recurrence

LARS Score

The LARS score is a validated, 5-item scoring system to evaluate bowel function in patients after anterior resection for rectal cancer (The score is available in a number of languages, including: English, German, Spanish, Swedish and Chinese (7-9).

Primary Outcome:

Incidence of low anterior resection syndrome, measured using a binary outcome (Y/N).

Secondary Outcome

- LARS score (0-42)
- Categorical LARS score (No LARS, Minor LARS, Major LARS)

Data:

Data already collected for the main ROLARR study will be used including :

- Patient demographics (age, sex, BMI)
- Cancer characteristics (level above anal verge, T-,N-, R-,M-stage, Duke's stage)
- Neoadjuvant radiotherapy
- Operation: robotic or laparoscopic; high or low anterior resection)
- Type of anastomosis
- Defunctioning stoma (ileostomy, colostomy)
- Complications, including anastomotic leak
- Adjuvant radiotherapy
- Interval to temporary stoma reversal
- Length of follow-up (time from restoration of GI continuity)
- Operating surgeon

The primary and secondary outcome measures will be summarised using descriptive statistics. χ^2 tests, unpaired t tests, ANOVA and non-parametric methods such as the Mann-Whitney U test and Kruskal-Wallis test will be used as appropriate to assess the statistical significance of crude associations between observed LARS outcomes and covariates of interest (see "Data" section)..

Multi-level logistic regression analysis as will be used to examine the influence of variables of interest on the primary outcome measure, adjusting for operating surgeon and other prognostic factors, with results expressed as adjusted odds ratios (ORs) with 95% confidence intervals (CI). Variables which are considered clinically plausible will be entered into the models, regardless of statistical significance at univariable level. Given sufficient patient numbers, and sufficient heterogeneity of follow-up times, the effect of follow-up time on LARS will also be explored in the analysis.

Outputs & Dissemination

Results will be presented at national scientific conferences and published in a peer-reviewed surgical journal.

References

1. Ferlay J. Steliarova-Foucher E. Lortet-Tieulent J. et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;**49**:1374–1403.
2. Bryant CL. Lunniss PJ. Knowles CH. et al. Anterior resection syndrome. *Lancet Oncol*. 2012;**13**:e403–e408.
3. Emmertsen KJ. Laurberg S. Bowel dysfunction after treatment for rectal cancer. *Acta Oncol*. 2008;**47**:994–1003.
4. Dinnewitzer A. Jager T. Nawara C. et al. Cumulative incidence of permanent stoma after sphincter preserving low anterior resection of mid and low rectal cancer. *Dis Colon Rectum* 2013;**56**:1134-42.
5. Pachler J. Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane Database Syst Rev*. 2005:CD004323.
6. Emmertsen KJ. Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg*. 2012;**255**:922– 928.
7. Juul T. Ahlberg M. Biondo S. et al. International validation of low anterior resection score. *Ann Surg*. 2014;**259**:728– 734

8. Juul T. Battersby NJ. Christensen P. et al. Validation of the English Translation of the Low Anterior Resection Syndrome Score (The LARS score). *Colorectal Dis* 2015 doi: 10.1111/codi.12952 [Epub]
9. Hou XT. Pang D. Lu Q. et al. Validation of the Chinese version of the low anterior resection syndrome score for measuring bowel dysfunction after sphincter-preserving surgery among rectal cancer patients. *Eur j Oncol Nurs* 2015 doi: 10.1016/j.ejon.2015.02.009. [Epub ahead of print]



Clinical Trials Research Unit (CTRU)
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds LS2 9JT
<http://ctr.u.leeds.ac.uk>

ROLARR Protocol: Summary of Changes

Version & Date	Summary of Changes
V1.0, dated 17 th Feb 2010	n/a- Original protocol submitted for ethical review
V2.0 dated 25 th Mar 2010	Changes were required to the PIS/ICF document following ethical review, protocol was upversioned to match revised version of PIS/ICF (no changes made to the protocol)
V3.0 dated 2 nd Aug 2010	<ul style="list-style-type: none"> • Contents and references updated. • Clarification of eligibility criteria. • Surgeon eligibility: It was initially stipulated that surgeons must have performed at least 15 rectal cancer resections per annum and have prior experience of at least 10 robotic-assisted rectal cancer resections. It was felt that to ensure the 'learning curve' effect does not bias the trial data, only surgeons who had performed at least 30 rectal cancer resections, with a minimum of 10 of these to be standard laparoscopic procedures, and 10 of these robotic assisted procedures, should be included in the trial to ensure surgeon competency in both arms of the trial. • BMI added as a stratification factor due to recent publications that BMI may be associated with an increased risk of conversion to open surgery. • Schedule of Events modified for clarity. • Pathology section updated including collection of extra tumour samples for tissue banking (explicit consent will be obtained) • Update of Study Organisational Structure diagram (section 17) • Clarification of pathology appendix (section 20) • Minor administrative changes
V4.0, dated 1 st Mar 2011	<ul style="list-style-type: none"> • Funder (EME) requested changes to reference to EME and removal of logos on front cover. • Contacts and table of contents updated. • Section 2 and 19: Addition of publication as it is now published. • Section 4 Eligibility: clarifications to procedures following feedback from the international trial launch meetings. • Section 5.2 Randomisation: clarification of timings following feedback from the international launch meetings. • Table 1: expedited safety reporting timeline revised to 30 days (correction to previous version). • Clarification added that all procedures will be video'd and the CTRU will inform sites which procedures to submit. • Pregnancy statement added. • Section 7.5 and Appendix 1: clarifications have been made to pathology processes following consultation with a trial pathologist following the analysis of the first trial specimen. Also procedures for submitting the slides for trial purposes and extra tumour/normal tissue blocks as an optional separate study were updated to ensure HTA compliance and clarity in procedures. • Section 7.7: Clarification of annual follow-up timing and addition of stoma details • Section 7.9 Pregnancy: Section added to ensure patients who may become pregnant on trial are handled correctly. • Section 7.12: End of study definition included as was omitted in previous version of protocol. • Section 8: Safety updates following feedback from the international launch meetings. Clarification of timing for expedited safety reports. • Section 8.5 and 15.1: Sections regarding procedures/responsibilities for Serious Breaches of GCP added in line with the latest CTRU policies. • Section 16 indemnity: updated following discussion with the insurers. • Section 17.2 Responsibilities: LImm responsibilities added regarding the central pathology assessment and optional separate tissue block study. • Section 18: Clarification to publication policy as journal author restrictions may be in place. • Section 23 Abbreviations: updated.

<p>V5.0, dated 19th Mar 2014</p>	<ul style="list-style-type: none"> • Contacts update • Removal of secondary endpoint: Global Operative Assessment of Laparoscopic Skills tool (GOALS). It was planned that an assessment of surgical skills would be carried out using the GOALS assessment. Videos were to be taken of the complete mesorectal dissection from all cases inclusive of both laparoscopic and robotic operations however this proved to be unfeasible due to the large size of the files. • Clarification of inclusion criteria surrounding diagnosis of rectal cancer amenable to curative surgery. The inclusion criteria states that a T-staging of 1-3 is a component of a patient being “amenable to curative surgery” for the purpose of this trial. This has been discussed by the Trial Management Group who agreed that the decision of the team to perform surgery acts as a sufficient indication that the patient is amenable to curative surgery. Therefore T-staging of 1-3 is a guide only, to reflect this ‘i.e.’ was removed and replaced with ‘for example • Specified that histopathology reports are only to be collected if reported in English • Clarification to assessment of Unexpected Serious Complications: CI can upgrade or downgrade assessment in the event of disagreement between local assessment in line with CTRU standard guidance • Increase in sample size. Following a successful extension request, the trial recruited to target ahead of the revised milestones, and the opportunity to recruit further patients within the revised timelines and budget was taken to maximise study power. The sample size was amended from 400 to a maximum of 520 participants to increase the power of the study from 80% to a maximum of 90% power. • Removal of South-East Asian Spoke to reflect actual spoke arrangements. The S.E. Asian spoke were unable to secure additional funding for them to deliver the CTU spoke function in Singapore, so were unable to act as a spoke. CTRU, Leeds (i.e. the Hub) co-ordinates centres in South East Asia and sites across the rest of the world (with the exception of sites in the US who are coordinated by the North American Spoke) • Neo-adjuvant therapy: Clarification that eligibility should be reassessed on completion of neo-adjuvant therapy and guidance added on timing of consent. • Analyses on a surgeon basis: additional wording added to expand on planned analyses (wording omitted in error from previous protocols) • Expected complications list expanded and grouped into relevant categories • Minor administrative changes
<p>V6.0, dated 1st Jul 2015</p>	<p>This amendment to the protocol was to include an additional one off questionnaire as a supplementary study to the ROLARR trial to determine the incidence and severity of Low Anterior Resection Syndrome (LARS) within participants of the ROLARR trial. The results will have important consequences when counselling future patients with rectal cancer on the likely functional outcomes of surgery. The protocol was amended to include an additional appendix (appendix 4) to cover the Low Anterior Resection Syndrome (LARS) supplementary study. Eligible ROLARR participants from Denmark, Germany, Italy, the US and the UK will be invited to complete a one off postal survey.</p>

**CLINICAL TRIALS RESEARCH UNIT
(CTRU)**

UNIVERSITY OF LEEDS

**STATISTICAL ANALYSIS PLAN:
SHORT-TERM ENDPOINTS ONLY**

ROLARR

**ROBOTIC VERSUS LAPAROSCOPIC RESECTION
FOR RECTAL CANCER**

VERSION 1.0

JANUARY 2015

Trial Statistician: Neil Corrigan
Supervising Statistician: Julia Brown
Senior Trial Co-ordinator: Julie Croft
CTRU Principal Investigator: Julie Croft
Chief Investigator: Mr David Jayne

Table of Contents

1	Introduction	3
1.1	Aims.....	3
1.2	Design	3
1.3	Sample size and expected accrual	3
1.4	Planned analyses	4
2	Endpoints.....	4
2.1	Primary endpoint	4
2.2	Hypothesis to be investigated	5
2.2.1	Derivation of primary endpoint.....	5
2.3	Secondary endpoints.....	5
2.3.1	Hypothesis to be investigated.....	5
2.3.2	Derivation of secondary endpoints	6
2.3.3	Description of quality of life questionnaires	6
2.3.4	Missing data.....	8
2.3.5	Non standard circumstances	9
3	Populations.....	9
3.1	Eligibility.....	9
3.2	Intention to treat population.....	9
3.3	Quality of life population	10
3.4	Per protocol population	10
3.5	Sensitivity analysis populations	10
4	Data Handling	11
4.1	Data monitoring	11
4.2	Data validation.....	11
5	Data Analysis.....	12
5.1	General calculations	12
5.2	Analysis	12
5.2.1	Screening data.....	12
5.2.2	Withdrawals	12
5.2.3	Baseline characteristics	13
5.2.4	Primary endpoint.....	13
5.2.5	Key secondary endpoints	15
5.2.6	Further secondary endpoints.....	16
5.2.7	Further analyses	18
5.3	Safety	19
6	Reporting and Dissemination of the Results	19
7	References.....	20

8	Appendices	21
8.1	Appendix 1 Protocol violations and deviations.....	21
8.2	Appendix 2 Abbreviations used in the text.....	23
9	Approval of Analysis Plan	24

1 Introduction

1.1 Aims

The aim of this 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 are evaluated for short- and longer-term outcomes.

The key short-term outcomes 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, quality of life (QoL) assessment and analysis of cost-effectiveness are performed to aid evidence-based knowledge to inform NHS and other service providers and decision-makers. These short-term outcomes are 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 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. These longer term outcomes will be analysed after the last randomised patient has had 3-years of follow-up.

This document presents information on the analyses of short-term endpoints only.

1.2 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. Patients are randomised on a 1:1 basis using a computer-generated minimisation programme that incorporates a random element to receive either robotic-assisted or standard laparoscopic rectal cancer surgery. The follow-up period finishes 3 years after the final patient is randomised.

The trial is stratified by intended 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) and Body Mass Index (BMI) (underweight/normal, overweight, obese class I, obese class II and obese class III, according to the WHO categorisation (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html accessed 22/08/2011)).

1.3 Sample size and expected accrual

Original text

A total of 400 patients (200 in each arm) will be recruited into the trial over an 18-month period. It is anticipated that approximately 15 patients per month will be recruited in the first 6 months, with monthly recruitment increasing to approximately 25 patients in the final 12 months.

The sample size calculation has been based on ensuring sufficient numbers of patients are recruited to address the primary endpoint of conversion to open rectal resection. A relative reduction of at least 50% (in absolute terms, 25% to 12.5% in the robotic-assisted laparoscopic arm) is 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 (Guillou 2005; Guillou,

Quirke et al. 2005)(Guillou, Quirke et al. 2005). 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 are required using a two-group continuity corrected chi-squared test of equal proportions (nQuery Advisor® 6.01). 400 patients (200 per arm) will therefore be recruited to allow for early withdrawals, cross-over, protocol violations (e.g. benign tumours) and missing follow-up data.

The sample size of 400 patients is based on the primary endpoint, however it is also adequate to obtain meaningful conclusions regarding the key secondary endpoints of circumferential resection margin (CRM) positivity rate and 3-year local recurrence rate

Update

Recruitment to the original target sample size of 400 patients was completed 5 months earlier than planned, and was under budget. A plan to continue to recruit to ROLARR until the planned end of recruitment date, up to a maximum of 520 patients (which, under the original sample size assumptions, would provide 90% power to detect a difference of at least 12.5% in conversion rates between the arms) was endorsed by EME, the DMEC and the TSC. Consequently, a total of 471 patients had been randomised by the time the trial closed to recruitment. Under the original sample size assumptions, this provides around 86% power to detect a difference of at least 12.5% in conversion rates between the arms.

1.4 Planned analyses

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, at yearly intervals.

The DMEC could choose to stop the trial at any time should they see fit. 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. Should the trial be stopped prematurely, the DMEC and the TSC in discussion with the Trial Management Group (TMG) will be responsible in deciding the appropriate handling of additional data after trial cessation.

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 for longer-term outcomes.

This document presents information on the analyses of short-term endpoints only.

2 Endpoints

2.1 Primary endpoint

The primary endpoint is the rate of conversion to open surgery.

2.2 Hypothesis to be investigated

The null hypothesis to be investigated in terms of the primary endpoint is that there is no difference between the treatment arms with respect to rate of conversion to open surgery. The alternative hypothesis is that there is a difference between the treatment groups, with the expectation being that robotic-assistance facilitates laparoscopic rectal cancer surgery. The hypothesis for the primary endpoint will be tested at a 2-sided 0.05 significance level.

2.2.1 Derivation of primary endpoint

Conversion is defined as the use of a laparotomy wound for any part of the mesorectal dissection.

The decision to convert to an open operation will be at the discretion of the operating surgeon. Details relating to the planned and actual operation will be collected on the baseline and operative case report forms (CRFs). Reasons for any conversions will also be collected on the operative CRF and will include operative difficulty, operative complications, robotic malfunction/complications and other reasons as stated by the operating surgeon.

2.3 Secondary endpoints

The two key secondary endpoints are as follows:

- Pathological CRM positivity rates,
- 3-year local recurrence rates.

Further secondary endpoints include the following:

- Intra-operative complications,
- 30-day post-operative complications,
- 6-month post-operative complications,
- 30-day operative mortality,
- Patient self-reported bladder function,
- Patient self-reported sexual function,
- Patient self-reported generic health,
- Patient self-reported fatigue,
- Quality of the plane of surgery,
- Health economics evaluation (analysis of health economics endpoints will be undertaken by the health economist).

2.3.1 Hypothesis to be investigated

The null hypotheses to be investigated in terms of the secondary endpoints are that there is no difference between the treatment groups with respect to each individual endpoint listed in 2.3. The alternative hypotheses are that there is a difference between the treatment groups with respect to each individual endpoint listed in 2.3. Secondary endpoint analyses will be performed at 2-sided 0.05 significance levels.

The short-term outcomes will include assessment of technical ease of the operation, as determined by clear pathological resection margins as an indicator of surgical accuracy and improved oncological outcome. In addition, QoL assessment, intra- and post-operative complications 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-month follow-up.

2.3.2 Derivation of secondary endpoints

The proportion of patients who have a **positive circumferential resection margin** (CRM) will be calculated from the local histopathology review. Positive CRM is a distance of ≤ 1 mm of the cancer from the resection margin.

Intra-operative complications will be obtained from the operative CRF. These are defined as adverse events occurring during surgery related to the surgical and related procedures (e.g. anaesthetic). Data on **post-operative (30-day and 6-month) complications** will be obtained from Post-operative complications form related to the 30-day and 6-month post-operative follow-up assessment. 30-day and 6-month complications are defined as an adverse event occurring during the first 30-days and 6-months post-operatively and related to surgery and related procedures, e.g. anaesthetic. Data on **30-day operative mortality** will be obtained from the Notification of Death form.

Patient self-reported bladder function will be assessed by the patient self reported International Prostatic Symptom Score (I-PSS[®]). **Patient self-reported sexual function** will be assessed in males by the International Index of Erectile Function (IIEF) and in females by the Female Sexual Function Index (FSFI[®]) questionnaires. Data will be collected at baseline and at 6 months. Scoring will be performed using scoring manual for the questionnaires and overall score will be derived in the SAS program.

Patient self-reported generic health will be assessed by the patient self-reported Short-Form 36 version 2 (SF-36v2[®]) and **patient self-reported fatigue** will be assessed by the patient self-reported Multi-dimensional Fatigue Inventory (MFI-20[®]) questionnaire. Data will be collected at baseline, 30 days and 6 months. Scoring will be performed using scoring manual for the questionnaires and overall score will be derived in the SAS program.

Quality of the plane of surgery will be defined by the grading criteria using the local histological review. 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 anorectum below the levators. Thus for an AR there will be a single grade and for an APR there will be two grades. Quality of resection of the mesorectum can be assessed as muscularis propria plane, intramesorectal plane and mesorectal plane. Thus the quality of surgery of the anorectum below the levators can be assessed as levator plane, sphincteric plane and intrasphincteric/submucosal plane. Note that these are ordinal, and have been listed in order of high to low quality for each area respectively.

2.3.3 Description of quality of life questionnaires

2.3.3.1 International Prostatic Symptom Score (I-PSS[®])

The IPSS provides a standardised measurement of the subjective problems of the patient experiencing problems urinating. The maximum total sum from questions 1 -7 is 35:

0 – 7 points	Mild symptoms
8 - 19 points	Moderate symptoms
20 - 35 points	Severe symptoms

2.3.3.2 International Index of Erectile Function (IIEF)

IIEF is a 15-item, self-administered questionnaire scale that was developed for the assessment of

erectile function. Five response domains were identified:

Domain	Questions	Score Range	Minimum Score	Maximum Score
Erectile function	1, 2, 3, 4, 5, 15	0(or 1)*-5	1	30
Orgasmic function	9, 10	0-5	0	10
Sexual desire	11, 12	1-5	2	10
Intercourse satisfaction	6, 7, 8	0-5	0	15
Overall satisfaction	13, 14	1-5	2	10

*Some questions have 6 ordinal answers, some have 5. Those with 6 are scored 0-5; those with 5 are scored 1-5.

Specific scoring instructions for each question are given in Rosen et al (1997).

Erectile function total scores can be interpreted as follows:

- 0 - 6 Severe dysfunction
- 7 - 12 Moderate dysfunction
- 13 - 18 Mild to moderate dysfunction
- 19 - 24 Mild dysfunction
- 25 - 30 No dysfunction.

For intercourse satisfaction domain, total scores can be interpreted as:

- 0 - 3 Severe dysfunction
- 4 - 6 Moderate dysfunction
- 7 - 9 Mild to moderate dysfunction
- 10 - 12 Mild dysfunction
- 13 - 15 No dysfunction

For other domains, total scores can be interpreted as follows:

- 0 - 2 Severe dysfunction
- 3 - 4 Moderate dysfunction
- 5 - 5 Mild to moderate dysfunction
- 7 - 8 Mild dysfunction
- 9 - 10 No dysfunction

2.3.3.3 Female Sexual Function Index (FSFI®)

The FSFI is a brief questionnaire measure of sexual function in women. It was developed for the specific purpose of assessing domains of sexual function (e.g. sexual arousal, orgasm, satisfaction, pain) in clinical trials.

The individual domain scores and full scale (overall) score of the FSFI can be derived from the computational formula outlined in the table below. For individual domain scores, add the scores of

the individual items that comprise the domain and multiply the sum by the domain factor (see below). Add the six domain scores to obtain the full scale score. It should be noted that within the individual domains, a domain score of zero indicates that the subject reported having no sexual activity during the past month.

Domain	Questions	Score Range	Factor	Minimum Score	Maximum Score
Desire	1, 2	1 - 5	0.6	1.2	6.0
Arousal	3, 4, 5, 6	0 - 5	0.3	0	6.0
Lubrication	7, 8, 9, 10	0 - 5	0.3	0	6.0
Orgasm	11, 12, 13	0 - 5	0.4	0	6.0
Satisfaction	14, 15, 16	0 (or 1) - 5	0.4	0.8	6.0
Pain	17, 18, 19	0 - 5	0.4	0	6.0
Full Scale Score Range				2.0	36.0

2.3.3.4 Short-Form 36 version 2 (SF-36v2®)

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.

SF-36v2 scoring algorithm will be used for scoring.

2.3.3.5 Multidimensional Fatigue Inventory (MFI)

The Multidimensional Fatigue Inventory is a self-report instrument. It contains 20 statements which cover different aspects of fatigue.

These 20 items are organized in five scales:

- General Fatigue item: 1, 5, 12, 16
- Physical Fatigue item: 2, 8, 14, 20
- Reduced Activity item: 3, 6, 10, 17
- Reduced Motivation item: 4, 9, 15, 18
- Mental Fatigue item: 7, 11, 13, 19

The scores per item run from 1 to 5. A higher score indicates more fatigue. Therefore, the items indicative for fatigue need to be recoded (1=5, 2=4, 3=3, 4=2, 5=1). This concerns item: 2, 5, 9, 10, 13, 14, 16, 17, 18, 19.

For each scale a total score is calculated by summation of the scores of the individual items. Scores can range from the minimum of 4 to the maximum of 20. The use of a total score over all 20 items is not recommended.

2.3.4 Missing data

Attempts will be made to retrieve missing data via a thorough data cleaning process. Every effort will be made to obtain complete dates for all key data and missing dates will be monitored. Completely missing dates are expected to be very rare.

The nature of missing data in QOL data analyses will be investigated and appropriate methods used depending on the missingness mechanism. Missing data from the QOL questionnaires may be item non-response (some questions, but not all, are answered for a particular questionnaire) or unit non-response (whole questionnaire is missing). Item non-response will be dealt with as detailed in the scoring manuals of the particular questionnaires. The extent of unit non-response will be assessed and the missing data mechanism investigated. Observed covariates (e.g. death, complications) will be investigated in relation to responses to QoL questionnaires (response present or missing) to aid understanding of the missingness mechanism. Missing data will be expected to be missing at random (MAR) or missing completely at random (MCAR). If there is any suspicion that the missing data are related to the potential outcomes, the potential impact that a violation of the MAR assumption (i.e. data is MNAR) could have on the analysis will be explored (Fairclough, 2010) as part of the sensitivity analysis.

Item-level missingness in QOL questionnaires will be approached as stipulated by the scoring instructions for each individual questionnaire. After applying the relevant scoring instructions, if item-level missingness is still present, then a Multiple imputation (MI) approach will be considered, using chained equations (MICE) if multiple items are missing (White et al, 2011).

2.3.5 Non standard circumstances

There may be an occasion where a patient has an advanced cancer, metastatic spread or cancer not amenable to curative surgery at the time of randomisation (as confirmed from the pathology form or from correspondence) or a retrospective review of previous investigations to correctly determine the date suspected for a recurrence has led to a diagnosis of metastatic disease which precedes randomisation. In addition, there may be instances where a patient receiving neo-adjuvant therapy does not proceed to definitive surgery or where a patient has an incomplete tumour resection following initial surgery. The number of patients to whom this applies, and the reason why, will be summarised by arm.

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.

3 Populations

The primary analysis will be performed on an intention-to-treat (ITT) basis, where patients will be included according to the surgical procedure they were randomised to.

3.1 Eligibility

Patients will be considered eligible for the ROLARR trial if they fulfil all inclusion criteria and do not fulfil any exclusion criteria for the trial. All patients should remain in the trial after randomisation unless they actively withdraw. If a patient is found to be ineligible after randomisation they will still be included in the ITT analyses unless full consent to trial participation is withdrawn, and this is documented, or written informed consent has not been obtained. The number of patients not fulfilling each eligibility criterion will be summarised.

3.2 Intention to treat population

The intention-to-treat population will consist of all patients randomised into ROLARR regardless of whether they were eligible and/or remained in the trial. However, any patient who withdraws their

full consent to participation or written informed consent has not been obtained will not be included. It is anticipated that this will be an exceptionally rare eventuality, and will not therefore have an impact on the analysis results. In this population, patients will be grouped according to the treatment they were randomised to receive.

3.3 Quality of life population

In the assessment of quality of life data, all patients who consent to participation in the trial and for whom the validated translation of the QoL questionnaire is available are included in the quality of life population. Exclusion of patients for whose appropriate validated translations are not available is unlikely to present a threat to validity of inferences when comparing the arms, because the exclusion is unrelated to treatment allocation, and is expected to balance out between the arms.

3.4 Per protocol population

Sensitivity analyses will be considered for the populations of patients that exclude from the ITT population randomised patients who were found to be ineligible for the trial with respect to each inclusion/exclusion criteria, or who committed one or more major protocol violations or deviations (see appendix 1), if there are a considerable number of such patients.

3.5 Safety population

The safety population will consist of all randomised patients who received study treatment. However, any patient that a) withdraws FULL CONSENT, or b) written informed consent has not been obtained, will not be included in the safety analyses. Patients will be grouped according to treatment actually received.

3.6 Sensitivity analysis populations

Surgery actually received (3 arms)

Sensitivity analyses will be performed where patients will be included according to the surgery actually received (laparoscopic, robotic-assisted or converted to open surgery). Patients whose surgery was converted from robotic-assisted to laparoscopic surgery intra-operatively should be included in the laparoscopic actual procedure group. Patients whose surgery was converted from laparoscopic to robotic-assisted surgery should be included in the robotic-assisted actual procedure group. Patients who convert from robotic-assisted to open surgery intra-operatively and patients who convert from laparoscopic to open surgery intra-operatively should be included in the same group (converted to open surgery actual procedure group).

Surgery actually received (2 arms)

Sensitivity analyses will be performed where patients will be included according to the surgery actually received (laparoscopic or robotic-assisted surgery). These will essentially be taking the same approach as the “surgery actually received (3 arms)” sensitivity analyses, but will not include “open surgery” as a separate group. For example, patients who convert from robotic-assisted to open surgery will be included in the robotic-assisted surgery arm. In particular, this will allow us to perform this sensitivity analysis on the primary endpoint (conversion to open surgery).

Centrally reviewed pathology data

In the analysis for the pathology endpoints (CRM positivity rates and quality of the plane of surgery scores), local histopathology data is used. Sensitivity analysis for the CRM positivity and quality of the plane of surgery will be performed using centrally reviewed data only.

4 Data Handling

4.1 Data monitoring

Data will be monitored for quality and completeness by the CTRU and Spoke CTU in California. Missing data will be chased until they are received, until confirmed as not available, or until the trial is at analysis. All efforts will be made to ensure that as much of the data is present as possible and that reasons are obtained when data are unobtainable. A validation check program incorporated into the study database verifies the data and discrepancy reports are generated for resolution by site.

An independent DMEC will review the safety and ethics of the ROLARR trial once one hundred patients have been recruited to the trial or within the 12 months from the first DMEC meeting (whichever is sooner, unless any safety issues need to be raised earlier) and afterwards at approximately yearly intervals. Detailed unblinded reports containing a summary of recruitment, data collection, rates of conversion, complications and circumferential resection margin (CRM) positivity, and a review of unexpected serious complications (USCs) and deaths will be prepared and presented to the DMEC during recruitment and follow-up.

4.2 Data validation

The database validates most dates and data in line with the pre-programmed validation rules in real time, as data are entered. The Data Manager also checks that all data is complete, consistent and up-to-date. Reasons should be obtained when data is unobtainable. Key short term data items required for critical variables (i.e. data items which comprise the key primary and secondary endpoints of the rate of conversion to open surgery and pathological CRM positivity rates will also be checked by the Data Manager in their initial validation and are as follows:

- Treatment allocation
- Date of randomisation
- Surgeon (randomising treating surgeon)
- Gender
- Neoadjuvant therapy
- Patient height and weight
- Intended procedure
- Intraoperative conversions to open surgery
- Evidence of CRM involvement
- Date of assessment/completion

After the data are downloaded and read into permanent SAS datasets, the SAS data will be validated by the Data Manager by manually 100% checking data from the permanent SAS datasets as derived by the Trial Statistician against the data as seen on the database for a random sample of 5 patients from each form to ensure the database is set up correctly and the data download has been successful.

SAS will also be used to validate the data and identify any inconsistent or missing data. Checks to be performed include:

- Eligibility criteria checks
- Death / complication dates in relation to randomisation dates
- Death / complication dates in relation to follow-up dates

- Other sequential dates
- Checks for unusual and outlying data
- Checks for missing data
- Other checks as deemed appropriate.

Any suspicious or inconsistent data identified via these checks will be noted and the Data Managers will be notified. All queries will be recorded in the Statistician's Trial File. The Trial Co-ordinators and/or Data Managers will check such inconsistencies against the patient forms. If there has been an error in data input causing such inconsistencies this will be corrected on the database. If there has been no error in data input, a query requesting clarification will be sent to site by the Trial Co-ordinators and/or Data Managers. Details of corresponding changes will be documented.

5 Data Analysis

5.1 General calculations

For summaries of population characteristics, all percentages will be calculated using the total number of patients or forms expected as the denominator (i.e. including all patients with missing data for that variable). Summaries of outcomes, such as conversion to open surgery, will not include patients with missing data in the denominator when calculating percentages. When patients with missing data are not included in the denominator, the number of patients included in the summary will be clearly presented. All percentages, means, medians, interquartile ranges and also ranges will be rounded to 1 decimal place (or 1 significant figure for numbers less than 1), whilst standard deviations will be rounded to 2 decimal places (or 2 significant figures for numbers less than 1). P-values will be rounded to 4 decimal places (those less than 0.0001 will be displayed as <0.0001), whilst parameter estimates, standard errors, hazard ratios and 95% confidence intervals will be reported to 2 decimal places (or 2 significant figures for numbers less than 1). All analyses will be carried out using SAS unless otherwise stated. Hypothesis testing will be 2-sided and at the 5% significance level unless stated otherwise. Values that are below the limit of detection e.g. ≤ 0.2 and are therefore non-quantifiable will be summarised using the limit of quantification value. For example for ≤ 0.2 , 0.2 would be substituted in the summary; however for listings (if required) the non-quantifiable value would be reported as an inequality e.g. ≤ 0.2 .

5.2 Analysis

5.2.1 Screening data

The CONSORT flow diagram will be used to summarise the course of participants through the study.

Participating sites are asked to record details of all participants screened for eligibility who are not registered, either because they are ineligible, or because they decline participation. The number of withdrawals of consent to the study will be summarised, along with reasons for withdrawal. The information on non-randomised participants will be summarised from the Screening log.

Protocol violations, if any, will be summarised, including violations of eligibility criteria on entry into the study and subsequent deviations from the protocol.

5.2.2 Withdrawals

The summary will include number, timings of and reasons for (where available) withdrawal of treatment and/or withdrawal of follow-up.

5.2.3 Baseline characteristics

Baseline patient and clinical data as recorded on the randomisation and baseline assessment forms will be tabulated using frequencies and summary statistics for each treatment group and overall. Missing or unobtainable data will be included as missing unless data are available from the 24-hour randomisation form. Local pathology details will also be summarised using frequencies and summary statistics for each treatment arm and overall. Missing or unobtainable local pathology data will be included as missing unless data are available from the central pathology review. No statistical testing will be carried out on these data.

For QoL questionnaires, the percentage of patients not completing each score (SF-36v2™, MF®I-20), EQ-5D©, I-PSS© and IIEF/FSFI©) at baseline will be summarised overall and by treatment arm. The number of non-responders for each individual item within each score will also be summarised overall and by arm.

5.2.4 Primary endpoint

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 multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering.

Treatment and covariate estimates with corresponding standard errors, 95% confidence intervals and p-values will be calculated. The treatment effect will be expressed as an odds ratio, with corresponding 95% confidence intervals of the differences in conversion rates to open surgery. Residuals and predicted values will be examined to assess the assumptions and fit of the statistical model.

The proportion of patients who convert between robotic-assisted and laparoscopic surgery intra-operatively will also be summarised.

Sensitivity analysis – Additional covariates

Sensitivity analyses will be performed to consider additional covariates thought to be potentially related to patient outcomes (identified via *a priori* clinical reasoning) for inclusion in the primary analysis regression model. These additional covariates are:

- Fixity of tumour
- Whether or not the tumour is an obstructing tumour
- T-staging (post neo-adjuvant therapy if applicable)
- N-staging (post neo-adjuvant therapy if applicable)
- Whether or not the patient had abdominal surgery prior to their ROLARR operation, and the level of scarring.
- Whether or not adhesions were identified.
- Whether or not there was a tumour perforation (non-iatrogenic)/abscess.

These additional covariates will be considered by first assessing imbalance across the treatment arms with respect to each one and performing exploratory analysis of the potential association of each one with the primary endpoint. A (non-automated) forward stepwise regression approach, beginning with the primary analysis model and considering the inclusion of the additional

covariates, will be taken. Inclusion of additional covariates will be determined primarily by the result of a likelihood ratio test comparing the model with and without the covariate, considering $p \leq 0.1$ to indicate a sufficient improvement in model fit. Once a final model is arrived at, any additional covariates included will be justified and, if they have notably impacted the location and/or precision of the treatment effect estimate, then the potential mechanism will be considered and discussed. Checking of model assumptions and fit will be carried out as for the primary analysis model.

Sensitivity analysis - Missing data

If a complete case analysis discards a substantial (>5%) proportion of patients, or is otherwise considered to be dubious due to violation of the implicit MCAR assumption (e.g. if the missingness can be reasonably well predicted from the observed data), then a sensitivity analysis will be considered to account for missing data. Approaches to assess the validity of the MCAR assumption will include summarising prognostic factors between those patients who are included and excluded (due to missing data) from the complete case analysis and fitting logistic regression models to indicators of missingness to determine whether the missingness can be reasonably predicted by the observed data (Fairclough, 2010).

Multiple imputation (MI) will be considered, and if the missing data occurs over multiple variables in the model then MI using chained equations (MICE) will be considered. If, via exploratory analysis and/or clinical reasoning, the missing data mechanism appears to be MNAR, then sensitivity analyses will be performed to explore the potential impact of the MNAR mechanism on the results (Fairclough 2010). The parameterisation of the difference between the distributions of observed and non-observed values will follow from the exploratory analysis and clinical reasoning, as a parameterisation that represents a clinically feasible range of scenarios will be applied.

Sensitivity analysis – Actual operating surgeon

The primary analysis will adjust for the stratification factors i.e. the values of those factors that were used in the stratification, regardless of whether those values were correct. In some cases, patients may have been stratified under incorrect stratification factors. In particular, their intended operating surgeon (used for stratification) may not have been their actual operating surgeon. We may expect that actual operating surgeon will have a more pronounced effect on patient outcomes than intended operating surgeon, particularly if there are many discrepancies between the two. Therefore, a sensitivity analysis will be performed which incorporates actual operating surgeon rather than intended operating surgeon as a covariate in the model.

Sensitivity analysis – Learning curve

Any potential learning curve effects will be investigated and adjusted for using a similar approach to that outlined by Cook et al (2004). For each surgeon, the number of robotic-assisted and laparoscopic colorectal operations relevant to ROLARR performed by that surgeon has been collected at regular intervals (no greater than 3 months) throughout the trial. From this, we will derive the number of ROLARR-relevant robotic-assisted and laparoscopic operations previously performed before each patient's operation, assuming that the timings of all counted previous operations are uniformly distributed across the interval in which they occurred. These patient-level covariates – “number of previous robotic operations” and “number of previous laparoscopic operations” – will be entered into the multi-level model used in the primary analysis as random effects to explore potential associations between increased numbers of operations and patient outcomes. Different functional forms of the numbers of operations performed will be considered for inclusion, since a learning curve effect may reasonably be expected to be non-linear (e.g. sigmoidal

or logarithmic). Interactions between the numbers of operations performed and the treatment effect will also be explored.

5.2.5 Key secondary endpoints

The differences in the proportion of patients who have a **positive circumferential resection margin** between the treatment groups will be compared using multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering.

Treatment and covariate estimates with corresponding standard errors, odds ratios, 95% confidence intervals and p-values will be calculated. The treatment effect will be expressed as an odds ratio, with corresponding 95% confidence intervals of the differences in pathological CRM positivity rates. Residuals and predicted values will be examined to assess the assumptions of the statistical model.

Sensitivity analysis – Additional covariates

Sensitivity analyses will be performed to consider additional covariates thought to be potentially related to patient outcomes (identified via *a priori* clinical reasoning) for inclusion in the primary analysis regression model. These additional covariates are:

- Fixity of tumour
- T-staging (post neo-adjuvant therapy)
- N-staging (post neo-adjuvant therapy)
- Whether or not there was a tumour perforation (non-iatrogenic)/abscess.
- Number of previous relevant operations performed by the operating surgeon.

These additional covariates will be considered for inclusion in the model using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Missing data

Sensitivity analyses will be considered to account for missing data. The approach to this will be as outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Learning curve

Any potential learning curve effects will be investigated and adjusted for using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Actual operating surgeon

Sensitivity of the results to the use of actual operating surgeon rather than intended operating surgeon (the stratification factor) will be explored using the approach outlined for the similar sensitivity analysis in section 5.2.4.

5.2.6 Further secondary endpoints

The differences in the proportion of patients who experience an **intra-operative complication** between the treatment groups will be compared using multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. The treatment effect will be expressed as an odds ratio and corresponding 95% 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 post-operative complication** between the treatment groups will be compared using multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. Odds ratios and corresponding 95% confidence intervals of the differences in a-30-day complication rates will be presented. Sensitivity analysis will be considered to account for missing data. The proportions of patients who have a 30-day 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 same approach as described for evaluating differences in the proportions of patients with 30-day post-operative complication between treatment groups will also be adopted for evaluating differences in the proportions of **patients with 6-month post-operative complications** between the treatment groups.

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 multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. 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 function** between the treatment groups at 6 months post-operation, as assessed by the patient self-reported I-PSS© questionnaire, will be compared using adjusted for baseline mean scores and 95% confidence intervals for the overall symptom (bladder) and for each individual I-PSS© item, obtained from a multi-level random effects model adjusted for the stratification factors, treating operating surgeon as the unit of clustering. Residuals and predicted values will be examined to assess the assumptions of the statistical model. 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.

The differences in **sexual function** between the treatment groups at 6 months post-operation, as assessed by the patient self-reported IIEF (male) / FSFI© (female) questionnaires, will be compared using adjusted for baseline mean scores and 95% confidence intervals for the overall sexual function scores and for each sexual function domains, obtained from a multi-level random effects model adjusted for the stratification factors, treating operating surgeon as the unit of clustering. Residuals and predicted values will be examined to assess the assumptions of the statistical model. 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.

The differences in **generic health-related quality of life** between the treatment groups at 30 days and 6 months post-operation, as assessed by the patient self-reported SF-36v2™ questionnaire, will be summarised using adjusted for baseline mean scores and 95% confidence intervals for the SF-36v2™ summary measures and for each SF-36v2™ scale, obtained from a multi-level repeated

measures model adjusted for the stratification factors, treating surgeon as the level 3 unit of clustering, and patients as the level 2 unit of clustering for the repeated measures. 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.

The differences in **fatigue levels** between the treatment groups at 30 days and 6 months post-operation, as assessed by the patient self-reported MFI®-20 questionnaire, will be summarised using adjusted for baseline mean scores and 95% confidence intervals for the MFI®-20 global fatigue scores and for individual fatigue scales, obtained from a multi-level repeated measures model adjusted for the stratification factors, treating surgeon as the level 3 unit of clustering, and patients as the level 2 unit of clustering for the repeated measures. 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.

The differences between treatment groups in **the quality of the plane of surgery**, as assessed by the local histological review will be compared using multi-level ordered logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Initially, the proportional odds assumption of the model will be checked. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. Odds ratios and corresponding 95% confidence intervals of categories of the quality of the surgery plane will be presented. Sensitivity analysis will be considered to account for missing data.

Sensitivity analyses – Additional covariates

For the analyses outlined above for **intra-operative complications, 30-day and 6-month post-operative complications, 30 day mortality, bladder and sexual function, generic health-related quality of life and fatigue**, sensitivity analyses will be performed to consider additional covariates thought to be potentially related to patient outcomes (identified via *a priori* clinical reasoning) for inclusion in the model. The additional covariates to be analysed are summarised in the following table. Covariates are shown in the rows, and endpoints for which those additional covariates will be considered are shown in the columns. An X indicates that that covariate will be considered for that endpoint.

<u>Additional covariates</u>	Intra- and post-operative complications	30-day mortality	Bladder and sexual function	Generic health	Fatigue	Quality of the plane of surgery
Co-morbidities	X	X		X	X	
Immunosuppression		X		X		
Fixity of tumour	X		X			X
Obstructing tumour (Y/N)	X	X				
T-staging	X		X			X
N-staging	X		X			X
Previous abdominal surgery (Y/N)	X					
Total operation	X	X				

time						
Adhesions (Y/N)	X					
Preoperative Radiotherapy	X	X				X
Tumour perforation (non-iatrogenic)	X	X				X

These additional covariates will be considered for inclusion in the model using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analyses – Missing data

The approaches to considering sensitivity analyses to account for missing data for the further secondary endpoints discussed in this section will be as outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analyses – Learning curve

Any potential learning curve effects with respect to **intra-operative complications, 30-day and 6-month post-operative complications, 30 day mortality, bladder and sexual function, generic health-related quality of life and fatigue** will be investigated and adjusted for using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Actual operating surgeon

Sensitivity of the results to the use of actual operating surgeon rather than intended operating surgeon (the stratification factor) will be explored using the approach outlined for the similar sensitivity analysis in section 5.2.4.

5.2.7 Further analyses

It should be emphasised that the following statistical analyses may not have sufficient power to be able to make statistically robust conclusions. Caution must therefore be exercised in the reporting and interpretation of such analyses.

Subgroup analyses for the primary endpoint

A subgroup analysis will be performed to investigate **the effect of the operation performed** (high anterior resection, low anterior resection, abdominoperineal resection, other) on the treatment effect.

A subgroup analysis will be performed to investigate **the effect of gender** on the treatment effect.

A subgroup analysis will be performed to investigate **the effect of BMI** on the treatment effect.

A subgroup analysis to investigate **the effect of the region** where the surgery was performed (UK,

Mainland Europe, US, Asia & Australia) on the treatment effect will be performed.

Subgroup analyses for the key secondary endpoint

A subgroup analysis will be performed to investigate **the effect of gender** on the treatment effect on the rate of positive circumferential resection margin.

A subgroup analysis will be performed to investigate **the effect of BMI** on the treatment effect on the rate of positive circumferential resection margin.

A subgroup analysis will be performed to investigate **the effect of T-staging** on the treatment effect on the rate of positive circumferential resection margin.

5.3 Safety

5.3.1.1 USCs

Details of USCs occurring with 30 days of surgery will be reported by treatment group. The number of USCs, the number of patients with USCs and full details of complications in medical terms (if known) will be presented. The time from randomisation to USCs will also be included.

5.3.1.2 Deaths

The number of deaths and primary cause of deaths will be summarised by treatment group.

5.3.1.3 Pregnancy

The number of pregnancies (if any) will be summarised by treatment group.

6 Reporting and Dissemination of the Results

The ROLARR trial will be analysed in two stages; the first stage when the last patient finished their 6 months post-operative follow-up assessment and the second stage when the last patient has reached 3 years after randomisation. A full report of the analysis following the template laid out in this Statistical Analysis Plan will take place. It is estimated that this will take approximately six months for each analysis from the final download of the database.

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 Leads, 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.

7 References

1. Cook, J.A., Ramsay C.R., Fayers P. (2004). "Statistical evaluations of learning curve effects in surgical trials". Clinical trials 1:421
2. Fairclough, D. L. (2010). Design and Analysis of Quality of Life Studies in Clinical Trials, Second Edition, CRC Press.
3. Guillou, P. J., P. Quirke, et al. (2005). "Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial." The Lancet **365**(9472): 1718-1726.
4. Punt, C. J. A., M. Buyse, et al. (2007). "Endpoints in Adjuvant Treatment Trials: A Systematic Review of the Literature in Colon Cancer and Proposed Definitions for Future Trials." Journal of the National Cancer Institute **99**(13): 998-1003.
5. Rosen, R.C., et al., (1997) "The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction". Urology. **49**(6): p. 822-30.
6. Vassiliou, M. C., L. S. Feldman, et al. (2005). "A global assessment tool for evaluation of intraoperative laparoscopic skills." The American Journal of Surgery **190**(1): 107-113.
7. White IR, Royston P, Wood AM (2011). "Multiple imputation using chained equations: Issues and guidance for practice". Statistics in Medicine. 30(4):377-99.

8 Appendices

8.1 Appendix 1 Protocol violations and deviations

All randomised patients will be included in the intention-to-treat analyses, with the following exception: Any patient that a) withdraws FULL CONSENT, or b) written informed consent has not been obtained, will not be included in the intention-to-treat, per-protocol or safety analyses.

If any inclusion criteria answers are ‘no’ or any of the exclusion criteria answers are ‘yes’ then the patient will be classed as not fulfilling the eligibility criteria, unless any of the data collected on the CRFs confirm that the corresponding answer is incorrect. Note that any cases where an inclusion/exclusion criteria does not appear to have been met for a patient who was randomised is queried with site, so erroneous answers to inclusion/exclusion criteria which point to a protocol violation are expected to be corrected before final analysis.

The following tables outline protocol violations and deviations. Patients who have at least one major protocol violation or deviation will be excluded from the per-protocol population.

Criteria that can be checked against data collected MAJOR? (Y/N)

• Aged less than 18 years at randomisation	Y
• Patient’s disease is not rectal cancer as defined in the protocol (i.e. the distal extent of the adenocarcinoma is not at or within 15cm of the anal margin)	Y
• ASA physical status > 3	Y
• Clinical or radiological evidence of metastatic spread	Y
• Pregnancy	Y
• Benign lesions of the rectum	Y
• Benign or malignant diseases of the anal canal	Y
• Pathological evidence of complete response to neo-adjuvant therapy	N
• Patient did not undergo surgery	Y
• Actual operation performed was not one of High anterior resection, Low anterior resection or APR	N
• Actual procedure performed was not one of Standard laparoscopic surgery or Robotic-assisted surgery	Y
• Patient randomised to receive standard laparoscopic surgery, and did not withdraw from treatment, but was converted to robotic surgery intra-operatively	Y

Criteria that cannot be checked against data collectedMAJOR? (Y/N)

• Patient unable to provide written informed consent	Y
• Patient's disease not amenable to curative surgery	Y
• Patient's disease not suitable for both robotic-assisted and laparoscopic rectal resection.	Y
• Patient is not fit to undergo robotic-assisted surgery or standard laparoscopic surgery.	Y
• Locally advanced cancers not amenable to curative surgery, or requiring en bloc multi-visceral resection.	Y
• Synchronous colorectal tumours requiring multi-segment surgical resection	Y
• Co-existent inflammatory bowel disease	Y
• Concurrent or previous diagnosis of invasive cancer within 5 years that could confuse diagnosis.	Y
• 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.	Y
• Participation in other rectal cancer clinical trial relating to surgical technique.	Y

8.2 Appendix 2 Abbreviations used in the text

AR	anterior resection
APR	abdomino-perineal resection
BMI	Body Mass Index
CRF	case report form
CRM	circumferential resection margin
CTRU	Clinical Trials Research Unit
DMEC	Data Management and Ethics Committee
GOALS	Global operative assessment laparoscopic skills tool
IIEF	International Index of Erectile Function
I-PSS [®]	International Prostatic Symptom Score
ITT	Intention To Treat
FSFI [®]	Female Sexual Function Index
MAR	Missing at random
MCAR	Missing completely at random
MFI-20 [®]	Multi-dimensional Fatigue Inventory
MI	Multiple Imputation
MICE	Multiple Imputation using Chained Equations
MNAR	Missing not at random
QoL	Quality of Life
SDV	Source Data Verification
SF-36v2 [®]	Short-Form 36 version 2
TMG	Trial Management Group
TSC	Trial Steering Committee

9 Approval of Analysis Plan

Clinical Trials Research Unit (CTRU)

The following analysis plan for the ROLARR study has been approved by the following personnel. Any signed amendments to the plan will be filed with this document.

Trial Statistician: _____

Date: _____

Supervising Statistician: _____

Date: _____

Senior Trial Co-ordinator: _____

Date: _____

CTRU Principal Investigator: _____

Date: _____

Chief Investigator: _____

Date: _____

Additional information:

--

**CLINICAL TRIALS RESEARCH UNIT
(CTRU)**

UNIVERSITY OF LEEDS

**STATISTICAL ANALYSIS PLAN:
SHORT-TERM ENDPOINTS ONLY**

ROLARR

**ROBOTIC VERSUS LAPAROSCOPIC RESECTION
FOR RECTAL CANCER**

VERSION 2.0

FEBRUARY 2015

Trial Statistician: Neil Corrigan
Supervising Statistician: Julia Brown
Senior Trial Co-ordinator: Julie Croft
CTRU Principal Investigator: Julie Croft
Chief Investigator: Mr David Jayne

Table of Contents

1	Introduction	3
1.1	Aims	3
1.2	Design	3
1.3	Sample size and expected accrual	3
1.4	Planned analyses	4
2	Endpoints	4
2.1	Primary endpoint	4
2.2	Hypothesis to be investigated	5
2.2.1	Derivation of primary endpoint	5
2.3	Secondary endpoints	5
2.3.1	Hypothesis to be investigated	5
2.3.2	Derivation of secondary endpoints	6
2.3.3	Description of quality of life questionnaires	6
2.3.4	Missing data	9
2.3.5	Non standard circumstances	9
3	Populations	9
3.1	Eligibility	9
3.2	Intention to treat population	10
3.3	Quality of life population	10
3.4	Per protocol population	10
3.5	Sensitivity analysis populations	10
4	Data Handling	11
4.1	Data monitoring	11
4.2	Data validation	11
5	Data Analysis	12
5.1	General calculations	12
5.2	Analysis	12
5.2.1	Screening data	12
5.2.2	Withdrawals	13
5.2.3	Baseline characteristics	13
5.2.4	Primary endpoint	13
5.2.5	Key secondary endpoints	15
5.2.6	Further secondary endpoints	16
5.2.7	Further analyses	19
5.3	Safety	19
6	Reporting and Dissemination of the Results	20
7	References	20

8	Appendices	22
8.1	Appendix 1 Protocol violations and deviations.....	22
8.2	Appendix 2 Abbreviations used in the text.....	24
9	Approval of Analysis Plan	25

1 Introduction

1.1 Aims

The aim of this 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 are evaluated for short- and longer-term outcomes.

The key short-term outcomes 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, quality of life (QoL) assessment and analysis of cost-effectiveness are performed to aid evidence-based knowledge to inform NHS and other service providers and decision-makers. These short-term outcomes are 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 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. These longer term outcomes will be analysed after the last randomised patient has had 3-years of follow-up.

This document presents information on the analyses of short-term endpoints only.

1.2 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. Patients are randomised on a 1:1 basis using a computer-generated minimisation programme that incorporates a random element to receive either robotic-assisted or standard laparoscopic rectal cancer surgery. The follow-up period finishes 3 years after the final patient is randomised.

The trial is stratified by intended 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) and Body Mass Index (BMI) (underweight/normal, overweight, obese class I, obese class II and obese class III, according to the WHO categorisation (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html accessed 22/08/2011)).

1.3 Sample size and expected accrual

Original text

A total of 400 patients (200 in each arm) will be recruited into the trial over an 18-month period. It is anticipated that approximately 15 patients per month will be recruited in the first 6 months, with monthly recruitment increasing to approximately 25 patients in the final 12 months.

The sample size calculation has been based on ensuring sufficient numbers of patients are recruited to address the primary endpoint of conversion to open rectal resection. A relative reduction of at least 50% (in absolute terms, 25% to 12.5% in the robotic-assisted laparoscopic arm) is 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 (Guillou 2005; Guillou,

Quirke et al. 2005)(Guillou, Quirke et al. 2005). 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 are required using a two-group continuity corrected chi-squared test of equal proportions (nQuery Advisor® 6.01). 400 patients (200 per arm) will therefore be recruited to allow for early withdrawals, cross-over, protocol violations (e.g. benign tumours) and missing follow-up data.

The sample size of 400 patients is based on the primary endpoint, however it is also adequate to obtain meaningful conclusions regarding the key secondary endpoints of circumferential resection margin (CRM) positivity rate and 3-year local recurrence rate

Update

Recruitment to the original target sample size of 400 patients was completed 5 months earlier than planned, and was under budget. A plan to continue to recruit to ROLARR until the planned end of recruitment date, up to a maximum of 520 patients (which, under the original sample size assumptions, would provide 90% power to detect a difference of at least 12.5% in conversion rates between the arms) was endorsed by EME, the DMEC and the TSC. Consequently, a total of 471 patients had been randomised by the time the trial closed to recruitment. Under the original sample size assumptions, this provides around 86% power to detect a difference of at least 12.5% in conversion rates between the arms.

1.4 Planned analyses

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, at yearly intervals.

The DMEC could choose to stop the trial at any time should they see fit. 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. Should the trial be stopped prematurely, the DMEC and the TSC in discussion with the Trial Management Group (TMG) will be responsible in deciding the appropriate handling of additional data after trial cessation.

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 for longer-term outcomes.

This document presents information on the analyses of short-term endpoints only.

2 Endpoints

2.1 Primary endpoint

The primary endpoint is the rate of conversion to open surgery.

2.2 Hypothesis to be investigated

The null hypothesis to be investigated in terms of the primary endpoint is that there is no difference between the treatment arms with respect to rate of conversion to open surgery. The alternative hypothesis is that there is a difference between the treatment groups, with the expectation being that robotic-assistance facilitates laparoscopic rectal cancer surgery. The hypothesis for the primary endpoint will be tested at a 2-sided 0.05 significance level.

2.2.1 Derivation of primary endpoint

Conversion is defined as the use of a laparotomy wound for any part of the mesorectal dissection.

The decision to convert to an open operation will be at the discretion of the operating surgeon. Details relating to the planned and actual operation will be collected on the baseline and operative case report forms (CRFs). Reasons for any conversions will also be collected on the operative CRF and will include operative difficulty, operative complications, robotic malfunction/complications and other reasons as stated by the operating surgeon.

2.3 Secondary endpoints

The two key secondary endpoints are as follows:

- Pathological CRM positivity rates,
- 3-year local recurrence rates.

Further secondary endpoints include the following:

- Intra-operative complications,
- 30-day post-operative complications,
- 6-month post-operative complications,
- 30-day operative mortality,
- Patient self-reported bladder function,
- Patient self-reported sexual function,
- Patient self-reported generic health,
- Patient self-reported fatigue,
- Quality of the plane of surgery,
- Health economics evaluation (analysis of health economics endpoints will be undertaken by the health economist).

2.3.1 Hypothesis to be investigated

The null hypotheses to be investigated in terms of the secondary endpoints are that there is no difference between the treatment groups with respect to each individual endpoint listed in 2.3. The alternative hypotheses are that there is a difference between the treatment groups with respect to each individual endpoint listed in 2.3. Secondary endpoint analyses will be performed at 2-sided 0.05 significance levels.

The short-term outcomes will include assessment of technical ease of the operation, as determined by clear pathological resection margins as an indicator of surgical accuracy and improved oncological outcome. In addition, QoL assessment, intra- and post-operative complications 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-month follow-up.

2.3.2 Derivation of secondary endpoints

The proportion of patients who have a **positive circumferential resection margin** (CRM) will be calculated from the local histopathology review. Positive CRM is a distance of ≤ 1 mm of the cancer from the resection margin.

Intra-operative complications will be obtained from the operative CRF. These are defined as adverse events occurring during surgery related to the surgical and related procedures (e.g. anaesthetic). Data on **post-operative (30-day and 6-month) complications** will be obtained from Post-operative complications form related to the 30-day and 6-month post-operative follow-up assessment. 30-day and 6-month complications are defined as an adverse event occurring during the first 30-days and 6-months post-operatively and related to surgery and related procedures, e.g. anaesthetic. Data on **30-day operative mortality** will be obtained from the Notification of Death form.

Patient self-reported bladder function will be assessed by the patient self reported International Prostatic Symptom Score (I-PSS[®]). **Patient self-reported sexual function** will be assessed in males by the International Index of Erectile Function (IIEF) and in females by the Female Sexual Function Index (FSFI[®]) questionnaires. Data will be collected at baseline and at 6 months. Scoring will be performed using scoring manual for the questionnaires and overall score will be derived in the SAS program.

Patient self-reported generic health will be assessed by the patient self-reported Short-Form 36 version 2 (SF-36v2[®]) and **patient self-reported fatigue** will be assessed by the patient self-reported Multi-dimensional Fatigue Inventory (MFI-20[®]) questionnaire. Data will be collected at baseline, 30 days and 6 months. Scoring will be performed using scoring manual for the questionnaires and overall score will be derived in the SAS program.

Heterogeneity of timings of quality of life measures will be accounted for via the consideration of a time (from operation to date of questionnaire completion) covariate, as well as sensitivity analyses using strict boundaries for inclusion e.g. for the 6 month time point +/- 1 month may be used as boundaries for inclusion.

Quality of the plane of surgery will be defined by the grading criteria using the local histological review. 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 anorectum below the levators. Thus for an AR there will be a single grade and for an APR there will be two grades. Quality of resection of the mesorectum can be assessed as muscularis propria plane, intramesorectal plane and mesorectal plane. Thus the quality of surgery of the anorectum below the levators can be assessed as levator plane, sphincteric plane and intrasphincteric/submucosal plane. Note that these are ordinal, and have been listed in order of high to low quality for each area respectively.

2.3.3 Description of quality of life questionnaires

2.3.3.1 International Prostatic Symptom Score (I-PSS[®])

The IPSS provides a standardised measurement of the subjective problems of the patient experiencing problems urinating. The maximum total sum from questions 1 -7 is 35:

0 – 7 points	Mild symptoms
8 - 19 points	Moderate symptoms
20 - 35 points	Severe symptoms

2.3.3.2 International Index of Erectile Function (IIEF)

IIEF is a 15-item, self-administered questionnaire scale that was developed for the assessment of erectile function. Five response domains were identified:

Domain	Questions	Score Range	Minimum Score	Maximum Score
Erectile function	1, 2, 3, 4, 5, 15	0(or 1)*-5	1	30
Orgasmic function	9, 10	0-5	0	10
Sexual desire	11, 12	1-5	2	10
Intercourse satisfaction	6, 7, 8	0-5	0	15
Overall satisfaction	13, 14	1-5	2	10

*Some questions have 6 ordinal answers, some have 5. Those with 6 are scored 0-5; those with 5 are scored 1-5.

Specific scoring instructions for each question are given in Rosen et al (1997).

Erectile function total scores can be interpreted as follows:

- 0 - 6 Severe dysfunction
- 7 - 12 Moderate dysfunction
- 13 - 18 Mild to moderate dysfunction
- 19 - 24 Mild dysfunction
- 25 - 30 No dysfunction.

For intercourse satisfaction domain, total scores can be interpreted as:

- 0 - 3 Severe dysfunction
- 4 - 6 Moderate dysfunction
- 7 - 9 Mild to moderate dysfunction
- 10 - 12 Mild dysfunction
- 13 - 15 No dysfunction

For other domains, total scores can be interpreted as follows:

- 0 - 2 Severe dysfunction
- 3 - 4 Moderate dysfunction
- 5 - 5 Mild to moderate dysfunction
- 7 - 8 Mild dysfunction
- 9 - 10 No dysfunction

2.3.3.3 Female Sexual Function Index (FSFI®)

The FSFI is a brief questionnaire measure of sexual function in women. It was developed for the

specific purpose of assessing domains of sexual function (e.g. sexual arousal, orgasm, satisfaction, pain) in clinical trials.

The individual domain scores and full scale (overall) score of the FSFI can be derived from the computational formula outlined in the table below. For individual domain scores, add the scores of the individual items that comprise the domain and multiply the sum by the domain factor (see below). Add the six domain scores to obtain the full scale score. It should be noted that within the individual domains, a domain score of zero indicates that the subject reported having no sexual activity during the past month.

Domain	Questions	Score Range	Factor	Minimum Score	Maximum Score
Desire	1, 2	1 - 5	0.6	1.2	6.0
Arousal	3, 4, 5, 6	0 - 5	0.3	0	6.0
Lubrication	7, 8, 9, 10	0 - 5	0.3	0	6.0
Orgasm	11, 12, 13	0 - 5	0.4	0	6.0
Satisfaction	14, 15, 16	0 (or 1) - 5	0.4	0.8	6.0
Pain	17, 18, 19	0 - 5	0.4	0	6.0
Full Scale Score Range				2.0	36.0

2.3.3.4 Short-Form 36 version 2 (SF-36v2[®])

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.

SF-36v2 scoring algorithm will be used for scoring.

2.3.3.5 Multidimensional Fatigue Inventory (MFI)

The Multidimensional Fatigue Inventory is a self-report instrument. It contains 20 statements which cover different aspects of fatigue.

These 20 items are organized in five scales:

- General Fatigue item: 1, 5, 12, 16
- Physical Fatigue item: 2, 8, 14, 20
- Reduced Activity item: 3, 6, 10, 17
- Reduced Motivation item: 4, 9, 15, 18
- Mental Fatigue item: 7, 11, 13, 19

The scores per item run from 1 to 5. A higher score indicates more fatigue. Therefore, the items indicative for fatigue need to be recoded (1=5, 2=4, 3=3, 4=2, 5=1). This concerns item: 2, 5, 9, 10, 13, 14, 16, 17, 18, 19.

For each scale a total score is calculated by summation of the scores of the individual items. Scores can range from the minimum of 4 to the maximum of 20. The use of a total score over all 20 items is not recommended.

2.3.4 Missing data

Attempts will be made to retrieve missing data via a thorough data cleaning process. Every effort will be made to obtain complete dates for all key data and missing dates will be monitored. Completely missing dates are expected to be very rare.

The nature of missing data in QOL data analyses will be investigated and appropriate methods used depending on the missingness mechanism. Missing data from the QOL questionnaires may be item non-response (some questions, but not all, are answered for a particular questionnaire) or unit non-response (whole questionnaire is missing). Item non-response will be dealt with as detailed in the scoring manuals of the particular questionnaires. The extent of unit non-response will be assessed and the missing data mechanism investigated. Observed covariates (e.g. death, complications) will be investigated in relation to responses to QoL questionnaires (response present or missing) to aid understanding of the missingness mechanism. Missing data will be expected to be missing at random (MAR) or missing completely at random (MCAR). If there is any suspicion that the missing data are related to the potential outcomes, the potential impact that a violation of the MAR assumption (i.e. data is MNAR) could have on the analysis will be explored (Fairclough, 2010) as part of the sensitivity analysis.

Item-level missingness in QOL questionnaires will be approached as stipulated by the scoring instructions for each individual questionnaire. After applying the relevant scoring instructions, if item-level missingness is still present, then a Multiple imputation (MI) approach will be considered, using chained equations (MICE) if multiple items are missing (White et al, 2011).

2.3.5 Non standard circumstances

There may be an occasion where a patient has an advanced cancer, metastatic spread or cancer not amenable to curative surgery at the time of randomisation (as confirmed from the pathology form or from correspondence) or a retrospective review of previous investigations to correctly determine the date suspected for a recurrence has led to a diagnosis of metastatic disease which precedes randomisation. In addition, there may be instances where a patient receiving neo-adjuvant therapy does not proceed to definitive surgery or where a patient has an incomplete tumour resection following initial surgery. There may also be randomised patients whose disease is determined to be benign based on post-randomisation investigation. The number of patients to whom this applies, and the reason why, will be summarised by arm.

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.

3 Populations

The primary analysis will be performed on an intention-to-treat (ITT) basis, where patients will be included according to the surgical procedure they were randomised to.

3.1 Eligibility

Patients will be considered eligible for the ROLARR trial if they fulfil all inclusion criteria and do not fulfil any exclusion criteria for the trial. All patients should remain in the trial after randomisation unless they actively withdraw. If a patient is found to be ineligible after randomisation they will still be included in the ITT analyses unless full consent to trial participation is withdrawn, and this is documented, or written informed consent has not been obtained. The number of patients not fulfilling each eligibility criterion will be summarised.

3.2 Intention to treat population

The intention-to-treat population will consist of all patients randomised into ROLARR regardless of whether they were eligible and/or remained in the trial. However, any patient who withdraws their full consent to participation or written informed consent has not been obtained will not be included. It is anticipated that this will be an exceptionally rare eventuality, and will not therefore have an impact on the analysis results. In this population, patients will be grouped according to the treatment they were randomised to receive.

3.3 Quality of life population

In the assessment of quality of life data, all patients who consent to participation in the trial and for who the validated translation of the QoL questionnaire is available are included in the quality of life population. Exclusion of patients for whose appropriate validated translations are not available is unlikely to present a threat to validity of inferences when comparing the arms, because the exclusion is unrelated to treatment allocation, and is expected to balance out between the arms.

3.4 Per protocol population

Sensitivity analyses will be considered for the populations of patients that exclude from the ITT population randomised patients who were found to be ineligible for the trial with respect to each inclusion/exclusion criteria, or who committed one or more major protocol violations or deviations (see appendix 1), if there are a considerable number of such patients.

3.5 Safety population

The safety population will consist of all randomised patients who received study treatment. However, any patient that a) withdraws FULL CONSENT, or b) written informed consent has not been obtained, will not be included in the safety analyses. Patients will be grouped according to treatment actually received.

3.6 Sensitivity analysis populations

Surgery actually received (3 arms)

Sensitivity analyses will be performed where patients will be included according to the surgery actually received (laparoscopic, robotic-assisted or converted to open surgery). Patients whose surgery was converted from robotic-assisted to laparoscopic surgery intra-operatively should be included in the laparoscopic actual procedure group. Patients whose surgery was converted from laparoscopic to robotic-assisted surgery should be included in the robotic-assisted actual procedure group. Patients who convert from robotic-assisted to open surgery intra-operatively and patients who convert from laparoscopic to open surgery intra-operatively should be included in the same group (converted to open surgery actual procedure group).

Surgery actually received (2 arms)

Sensitivity analyses will be performed where patients will be included according to the surgery actually received (laparoscopic or robotic-assisted surgery). These will essentially be taking the same approach as the “surgery actually received (3 arms)” sensitivity analyses, but will not include “open surgery” as a separate group. For example, patients who convert from robotic-assisted to

open surgery will be included in the robotic-assisted surgery arm. In particular, this will allow us to perform this sensitivity analysis on the primary endpoint (conversion to open surgery).

Centrally reviewed pathology data

In the analysis for the pathology endpoints (CRM positivity rates and quality of the plane of surgery scores), local histopathology data is used. Sensitivity analysis for the CRM positivity and quality of the plane of surgery will be performed using centrally reviewed data only.

4 Data Handling

4.1 Data monitoring

Data will be monitored for quality and completeness by the CTRU and Spoke CTU in California. Missing data will be chased until they are received, until confirmed as not available, or until the trial is at analysis. All efforts will be made to ensure that as much of the data is present as possible and that reasons are obtained when data are unobtainable. A validation check program incorporated into the study database verifies the data and discrepancy reports are generated for resolution by site.

An independent DMEC will review the safety and ethics of the ROLARR trial once one hundred patients have been recruited to the trial or within the 12 months from the first DMEC meeting (whichever is sooner, unless any safety issues need to be raised earlier) and afterwards at approximately yearly intervals. Detailed unblinded reports containing a summary of recruitment, data collection, rates of conversion, complications and circumferential resection margin (CRM) positivity, and a review of unexpected serious complications (USCs) and deaths will be prepared and presented to the DMEC during recruitment and follow-up.

4.2 Data validation

The database validates most dates and data in line with the pre-programmed validation rules in real time, as data are entered. The Data Manager also checks that all data is complete, consistent and up-to-date. Reasons should be obtained when data is unobtainable. Key short term data items required for critical variables (i.e. data items which comprise the key primary and secondary endpoints of the rate of conversion to open surgery and pathological CRM positivity rates will also be checked by the Data Manager in their initial validation and are as follows:

- Treatment allocation
- Date of randomisation
- Surgeon (randomising treating surgeon)
- Gender
- Neoadjuvant therapy
- Patient height and weight
- Intended procedure
- Intraoperative conversions to open surgery
- Evidence of CRM involvement
- Date of assessment/completion

After the data are downloaded and read into permanent SAS datasets, the SAS data will be validated by the Data Manager by manually 100% checking data from the permanent SAS datasets as derived by the Trial Statistician against the data as seen on the database for a random sample of 5 patients from each form to ensure the database is set up correctly and the data download has been successful.

SAS will also be used to validate the data and identify any inconsistent or missing data. Checks to be performed include:

- Eligibility criteria checks
- Death / complication dates in relation to randomisation dates
- Death / complication dates in relation to follow-up dates
- Other sequential dates
- Checks for unusual and outlying data
- Checks for missing data
- Other checks as deemed appropriate.

Any suspicious or inconsistent data identified via these checks will be noted and the Data Managers will be notified. All queries will be recorded in the Statistician's Trial File. The Trial Co-ordinators and/or Data Managers will check such inconsistencies against the patient forms. If there has been an error in data input causing such inconsistencies this will be corrected on the database. If there has been no error in data input, a query requesting clarification will be sent to site by the Trial Co-ordinators and/or Data Managers. Details of corresponding changes will be documented.

5 Data Analysis

5.1 General calculations

For summaries of population characteristics, all percentages will be calculated using the total number of patients or forms expected as the denominator (i.e. including all patients with missing data for that variable). Summaries of outcomes, such as conversion to open surgery, will not include patients with missing data in the denominator when calculating percentages. When patients with missing data are not included in the denominator, the number of patients included in the summary will be clearly presented. All percentages, means, medians, interquartile ranges and also ranges will be rounded to 1 decimal place (or 1 significant figure for numbers less than 1), whilst standard deviations will be rounded to 2 decimal places (or 2 significant figures for numbers less than 1). P-values will be rounded to 4 decimal places (those less than 0.0001 will be displayed as <0.0001), whilst parameter estimates, standard errors, hazard ratios and 95% confidence intervals will be reported to 2 decimal places (or 2 significant figures for numbers less than 1). All analyses will be carried out using SAS unless otherwise stated. Hypothesis testing will be 2-sided and at the 5% significance level unless stated otherwise. Values that are below the limit of detection e.g. ≤ 0.2 and are therefore non-quantifiable will be summarised using the limit of quantification value. For example for ≤ 0.2 , 0.2 would be substituted in the summary; however for listings (if required) the non-quantifiable value would be reported as an inequality e.g. ≤ 0.2 .

5.2 Analysis

5.2.1 Screening data

The CONSORT flow diagram will be used to summarise the course of participants through the study.

Participating sites are asked to record details of all participants screened for eligibility who are not registered, either because they are ineligible, or because they decline participation. The number of withdrawals of consent to the study will be summarised, along with reasons for withdrawal. The information on non-randomised participants will be summarised from the Screening log.

Protocol violations, if any, will be summarised, including violations of eligibility criteria on entry into the study and subsequent deviations from the protocol.

5.2.2 Withdrawals

The summary will include number, timings of and reasons for (where available) withdrawal of treatment and/or withdrawal of follow-up.

5.2.3 Baseline characteristics

Baseline patient and clinical data as recorded on the randomisation and baseline assessment forms will be tabulated using frequencies and summary statistics for each treatment group and overall. Missing or unobtainable data will be included as missing unless data are available from the 24-hour randomisation form. Local pathology details will also be summarised using frequencies and summary statistics for each treatment arm and overall. No statistical testing will be carried out on these data.

For QoL questionnaires, the percentage of patients not completing each score (SF-36v2™, MF®I-20), EQ-5D®, I-PSS® and IIEF/FSFI®) at baseline will be summarised overall and by treatment arm. The number of non-responders for each individual item within each score will also be summarised overall and by arm.

5.2.4 Primary endpoint

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 multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering.

Treatment and covariate estimates with corresponding standard errors, 95% confidence intervals and p-values will be calculated. The treatment effect will be expressed as an odds ratio, with corresponding 95% confidence intervals of the differences in conversion rates to open surgery. Residuals and predicted values will be examined to assess the assumptions and fit of the statistical model.

The analysis will be a complete case analysis. See below (sensitivity analysis – missing data) for details on how missing data will be approached.

The proportion of patients who convert between robotic-assisted and laparoscopic surgery intra-operatively will also be summarised.

Sensitivity analysis – Additional covariates

Sensitivity analyses will be performed to consider additional covariates thought to be potentially related to patient outcomes (identified via *a priori* clinical reasoning) for inclusion in the primary analysis regression model. These additional covariates are:

- Fixity of tumour
- Whether or not the tumour is an obstructing tumour
- T-staging
- N-staging
- Whether or not the patient had abdominal surgery prior to their ROLARR operation, and the level of scarring.

- Whether or not adhesions were identified.
- Whether or not there was a tumour perforation (non-iatrogenic)/abscess.

These additional covariates will be considered by first assessing imbalance across the treatment arms with respect to each one and performing exploratory analysis of the potential association of each one with the primary endpoint. A (non-automated) forward stepwise regression approach, beginning with the primary analysis model and considering the inclusion of the additional covariates, will be taken. Inclusion of additional covariates will be determined primarily by the result of a likelihood ratio test comparing the model with and without the covariate, considering $p \leq 0.1$ to indicate a sufficient improvement in model fit. Once a final model is arrived at, any additional covariates included will be justified and, if they have notably impacted the location and/or precision of the treatment effect estimate, then the potential mechanism will be considered and discussed. Checking of model assumptions and fit will be carried out as for the primary analysis model.

Sensitivity analysis - Missing data

If a complete case analysis discards a substantial (>5%) proportion of patients, or is otherwise considered to be dubious due to violation of the implicit MCAR assumption (e.g. if the missingness can be reasonably well predicted from the observed data), then a sensitivity analysis will be considered to account for missing data. Approaches to assess the validity of the MCAR assumption will include summarising prognostic factors between those patients who are included and excluded (due to missing data) from the complete case analysis and fitting logistic regression models to indicators of missingness to determine whether the missingness can be reasonably predicted by the observed data (Fairclough, 2010).

Multiple imputation (MI) will be considered, and if the missing data occurs over multiple variables in the model then MI using chained equations (MICE) will be considered. If, via exploratory analysis and/or clinical reasoning, the missing data mechanism appears to be MNAR, then sensitivity analyses will be performed to explore the potential impact of the MNAR mechanism on the results (Fairclough 2010). The parameterisation of the difference between the distributions of observed and non-observed values will follow from the exploratory analysis and clinical reasoning, as a parameterisation that represents a clinically feasible range of scenarios will be applied.

Sensitivity analysis – Actual operating surgeon

The primary analysis will adjust for the stratification factors i.e. the values of those factors that were used in the stratification, regardless of whether those values were correct. In some cases, patients may have been stratified under incorrect stratification factors. In particular, their intended operating surgeon (used for stratification) may not have been their actual operating surgeon. We may expect that actual operating surgeon will have a more pronounced effect on patient outcomes than intended operating surgeon, particularly if there are many discrepancies between the two. Therefore, a sensitivity analysis will be performed which incorporates actual operating surgeon rather than intended operating surgeon as a covariate in the model.

Sensitivity analysis – Learning curve

Any potential learning curve effects will be investigated and adjusted for using a similar approach to that outlined by Cook et al (2004). For each surgeon, the number of robotic-assisted and laparoscopic colorectal operations relevant to ROLARR performed by that surgeon has been collected at regular intervals (no greater than 3 months) throughout the trial. From this, we will

derive the number of ROLARR-relevant robotic-assisted and laparoscopic operations previously performed before each patient's operation, assuming that the timings of all counted previous operations are uniformly distributed across the interval in which they occurred. These patient-level covariates – “number of previous robotic operations” and “number of previous laparoscopic operations” – will be entered into the multi-level model used in the primary analysis as random effects to explore potential associations between increased numbers of operations and patient outcomes. Different functional forms of the numbers of operations performed will be considered for inclusion, since a learning curve effect may reasonably be expected to be non-linear (e.g. sigmoidal or logarithmic). Interactions between the numbers of operations performed and the treatment effect will also be explored.

Sensitivity analysis – Central pathology data

Local pathology data will be used to carry out the analyses. The agreement of local pathology and central pathology with respect to factors feeding into the analyses (e.g. T-staging) will be assessed. Analyses will be repeated using central pathology data instead of local pathology data if the level of agreement is considered to be insufficient.

5.2.5 Key secondary endpoint

The differences in the proportion of patients who have a **positive circumferential resection margin** between the treatment groups will be compared using multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering.

Treatment and covariate estimates with corresponding standard errors, odds ratios, 95% confidence intervals and p-values will be calculated. The treatment effect will be expressed as an odds ratio, with corresponding 95% confidence intervals of the differences in pathological CRM positivity rates. Residuals and predicted values will be examined to assess the assumptions of the statistical model.

The analysis will be a complete case analysis. See below (sensitivity analysis – missing data) for details on how missing data will be approached.

Sensitivity analysis – Additional covariates

Sensitivity analyses will be performed to consider additional covariates thought to be potentially related to patient outcomes (identified via *a priori* clinical reasoning) for inclusion in the primary analysis regression model. These additional covariates are:

- Fixity of tumour
- T-staging (post neo-adjuvant therapy)
- N-staging (post neo-adjuvant therapy)
- Whether or not there was a tumour perforation (non-iatrogenic)/abscess.
- Number of previous relevant operations performed by the operating surgeon.

These additional covariates will be considered for inclusion in the model using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Missing data

Sensitivity analyses will be considered to account for missing data. The approach to this will be as outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Learning curve

Any potential learning curve effects will be investigated and adjusted for using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Actual operating surgeon

Sensitivity of the results to the use of actual operating surgeon rather than intended operating surgeon (the stratification factor) will be explored using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Central pathology data

Sensitivity of the results to the use of central pathology data rather than local pathology data may be explored as described in section 5.2.4.

5.2.6 Further secondary endpoints

The differences in the proportion of patients who experience an **intra-operative complication** between the treatment groups will be compared using multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. The treatment effect will be expressed as an odds ratio and corresponding 95% 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 post-operative complication** between the treatment groups will be compared using multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. Odds ratios and corresponding 95% confidence intervals of the differences in a-30-day complication rates will be presented. Sensitivity analysis will be considered to account for missing data. The proportions of patients who have a 30-day 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 same approach as described for evaluating differences in the proportions of patients with 30-day post-operative complication between treatment groups will also be adopted for evaluating differences in the proportions of **patients with 6-month post-operative complications** between the treatment groups.

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 multi-level logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. 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 function** between the treatment groups at 6 months post-operation, as assessed by the patient self-reported I-PSS© questionnaire, will be compared using adjusted for baseline mean scores and 95% confidence intervals for the overall symptom (bladder) and for each individual I-PSS© item, obtained from a multi-level random effects model adjusted for the stratification factors, treating operating surgeon as the unit of clustering. Residuals and predicted values will be examined to assess the assumptions of the statistical model. 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.

The differences in **sexual function** between the treatment groups at 6 months post-operation, as assessed by the patient self-reported IIEF (male) / FSFI© (female) questionnaires, will be compared using adjusted for baseline mean scores and 95% confidence intervals for the overall sexual function scores and for each sexual function domains, obtained from a multi-level random effects model adjusted for the stratification factors, treating operating surgeon as the unit of clustering. Residuals and predicted values will be examined to assess the assumptions of the statistical model. 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.

The differences in **generic health-related quality of life** between the treatment groups at 30 days and 6 months post-operation, as assessed by the patient self-reported SF-36v2™ questionnaire, will be summarised using adjusted for baseline mean scores and 95% confidence intervals for the SF-36v2™ summary measures and for each SF-36v2™ scale, obtained from a multi-level repeated measures model adjusted for the stratification factors, treating surgeon as the level 3 unit of clustering, and patients as the level 2 unit of clustering for the repeated measures. 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.

The differences in **fatigue levels** between the treatment groups at 30 days and 6 months post-operation, as assessed by the patient self-reported MFI®-20 questionnaire, will be summarised using adjusted for baseline mean scores and 95% confidence intervals for the MFI®-20 global fatigue scores and for individual fatigue scales, obtained from a multi-level repeated measures model adjusted for the stratification factors, treating surgeon as the level 3 unit of clustering, and patients as the level 2 unit of clustering for the repeated measures. 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.

The differences between treatment groups in **the quality of the plane of surgery**, as assessed by the local histological review will be compared using multi-level ordered logistic regression adjusting for the stratification factors, treating operating surgeon as the unit of clustering. Initially, the proportional odds assumption of the model will be checked. Treatment and covariate estimates with corresponding standard errors, odds ratios and 95% confidence intervals and p-values will be calculated. Odds ratios and corresponding 95% confidence intervals of categories of the quality of the surgery plane will be presented. Sensitivity analysis will be considered to account for missing data.

Sensitivity analyses – Additional covariates

For the analyses outlined above for **intra-operative complications, 30-day and 6-month post-operative complications, 30 day mortality, bladder and sexual function, generic health-related quality of life, fatigue and quality of the plane of surgery**, sensitivity analyses will be performed to consider additional covariates thought to be potentially related to patient outcomes (identified via

a priori clinical reasoning) for inclusion in the model. The additional covariates to be analysed are summarised in the following table. Covariates are shown in the rows, and endpoints for which those additional covariates will be considered are shown in the columns. An X indicates that that covariate will be considered for that endpoint.

<u>Additional covariates</u>	Intra- and post-operative complications	30-day mortality	Bladder and sexual function	Generic health	Fatigue	Quality of the plane of surgery
Co-morbidities	X	X		X	X	
Immunosuppression		X		X		
Fixity of tumour	X		X			X
Obstructing tumour (Y/N)	X	X				
T-staging	X		X			X
N-staging	X		X			X
Previous abdominal surgery (Y/N)	X					
Total operation time	X	X				
Adhesions (Y/N)	X					
Preoperative Radiotherapy	X	X				X
Tumour perforation (non-iatrogenic)	X	X				X

These additional covariates will be considered for inclusion in the model using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analyses – Missing data

The approaches to considering sensitivity analyses to account for missing data for the further secondary endpoints discussed in this section will be as outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analyses – Learning curve

Any potential learning curve effects with respect to **intra-operative complications, 30-day and 6-month post-operative complications, 30 day mortality, bladder and sexual function, generic health-related quality of life, fatigue and quality of the plane of surgery** will be investigated and adjusted for using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Actual operating surgeon

Sensitivity of the results to the use of actual operating surgeon rather than intended operating

surgeon (the stratification factor) will be explored using the approach outlined for the similar sensitivity analysis in section 5.2.4.

Sensitivity analysis – Central pathology data

Sensitivity of the results to the use of central pathology data rather than local pathology data may be explored as described in section 5.2.4.

5.2.7 Further analyses

It should be emphasised that the following statistical analyses may not have sufficient power to be able to make statistically robust conclusions. Caution must therefore be exercised in the reporting and interpretation of such analyses.

Subgroup analyses for the primary endpoint

A subgroup analysis will be performed to investigate **the effect of the operation performed** (high anterior resection, low anterior resection, abdominoperineal resection, other) on the treatment effect.

A subgroup analysis will be performed to investigate **the effect of gender** on the treatment effect.

A subgroup analysis will be performed to investigate **the effect of BMI** on the treatment effect.

A subgroup analysis to investigate **the effect of the region** where the surgery was performed (UK, Mainland Europe, US, Asia & Australia) on the treatment effect will be performed.

Subgroup analyses for the key secondary endpoint

A subgroup analysis will be performed to investigate **the effect of gender** on the treatment effect on the rate of positive circumferential resection margin.

A subgroup analysis will be performed to investigate **the effect of BMI** on the treatment effect on the rate of positive circumferential resection margin.

A subgroup analysis will be performed to investigate **the effect of T-staging** on the treatment effect on the rate of positive circumferential resection margin.

5.3 Safety

5.3.1.1 USCs

Details of USCs occurring with 30 days of surgery will be reported by treatment group. The number of USCs, the number of patients with USCs and full details of complications in medical terms (if known) will be presented. The time from randomisation to USCs will also be included.

5.3.1.2 Deaths

The number of deaths and primary cause of deaths will be summarised by treatment group.

5.3.1.3 Pregnancy

The number of pregnancies (if any) will be summarised by treatment group.

6 Reporting and Dissemination of the Results

The ROLARR trial will be analysed in two stages; the first stage when the last patient finished their 6 months post-operative follow-up assessment and the second stage when the last patient has reached 3 years after randomisation. A full report of the analysis following the template laid out in this Statistical Analysis Plan will take place. It is estimated that this will take approximately six months for each analysis from the final download of the database.

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 Leads, 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.

7 References

1. Cook, J.A., Ramsay C.R., Fayers P. (2004). "Statistical evaluations of learning curve effects in surgical trials". Clinical trials 1:421
2. Fairclough, D. L. (2010). Design and Analysis of Quality of Life Studies in Clinical Trials, Second Edition, CRC Press.
3. Guillou, P. J., P. Quirke, et al. (2005). "Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial." The Lancet **365**(9472): 1718-1726.
4. Punt, C. J. A., M. Buyse, et al. (2007). "Endpoints in Adjuvant Treatment Trials: A Systematic Review of the Literature in Colon Cancer and Proposed Definitions for Future Trials." Journal of the National Cancer Institute **99**(13): 998-1003.
5. Rosen, R.C., et al., (1997) "The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction". Urology. **49**(6): p. 822-30.
6. Vassiliou, M. C., L. S. Feldman, et al. (2005). "A global assessment tool for evaluation of intraoperative laparoscopic skills." The American Journal of Surgery **190**(1): 107-113.
7. White IR, Royston P, Wood AM (2011). "Multiple imputation using chained equations: Issues and guidance for practice". Statistics in Medicine. 30(4):377-99.

8 Appendices

8.1 Appendix 1 Protocol violations and deviations

All randomised patients will be included in the intention-to-treat analyses, with the following exception: Any patient that a) withdraws FULL CONSENT, or b) written informed consent has not been obtained, will not be included in the intention-to-treat, per-protocol or safety analyses.

If any inclusion criteria answers are ‘no’ or any of the exclusion criteria answers are ‘yes’ then the patient will be classed as not fulfilling the eligibility criteria, unless any of the data collected on the CRFs confirm that the corresponding answer is incorrect. Note that any cases where an inclusion/exclusion criteria does not appear to have been met for a patient who was randomised is queried with site, so erroneous answers to inclusion/exclusion criteria which point to a protocol violation are expected to be corrected before final analysis.

The following tables outline protocol violations and deviations. Patients who have at least one major protocol violation or deviation will be excluded from the per-protocol population.

Criteria that can be checked against data collected MAJOR? (Y/N)

• Aged less than 18 years at randomisation	Y
• Patient’s disease is not rectal cancer as defined in the protocol (i.e. the distal extent of the adenocarcinoma is not at or within 15cm of the anal margin)	Y
• ASA physical status > 3	Y
• Clinical or radiological evidence of metastatic spread	Y
• Pregnancy	Y
• Benign lesions of the rectum	Y
• Benign or malignant diseases of the anal canal	Y
• Pathological evidence of complete response to neo-adjuvant therapy	N
• Patient did not undergo surgery	Y
• Actual operation performed was not one of High anterior resection, Low anterior resection or APR	N
• Actual procedure performed was not one of Standard laparoscopic surgery or Robotic-assisted surgery	Y
• Patient randomised to receive standard laparoscopic surgery, and did not withdraw from treatment, but was converted to robotic surgery intra-operatively	Y

Criteria that cannot be checked against data collectedMAJOR? (Y/N)

• Patient unable to provide written informed consent	Y
• Patient's disease not amenable to curative surgery	Y
• Patient's disease not suitable for both robotic-assisted and laparoscopic rectal resection.	Y
• Patient is not fit to undergo robotic-assisted surgery or standard laparoscopic surgery.	Y
• Locally advanced cancers not amenable to curative surgery, or requiring en bloc multi-visceral resection.	Y
• Synchronous colorectal tumours requiring multi-segment surgical resection	Y
• Co-existent inflammatory bowel disease	Y
• Concurrent or previous diagnosis of invasive cancer within 5 years that could confuse diagnosis.	Y
• 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.	Y
• Participation in other rectal cancer clinical trial relating to surgical technique.	Y

8.2 Appendix 2 Abbreviations used in the text

AR	anterior resection
APR	abdomino-perineal resection
BMI	Body Mass Index
CRF	case report form
CRM	circumferential resection margin
CTRU	Clinical Trials Research Unit
DMEC	Data Management and Ethics Committee
GOALS	Global operative assessment laparoscopic skills tool
IIEF	International Index of Erectile Function
I-PSS [®]	International Prostatic Symptom Score
ITT	Intention To Treat
FSFI [®]	Female Sexual Function Index
MAR	Missing at random
MCAR	Missing completely at random
MFI-20 [®]	Multi-dimensional Fatigue Inventory
MI	Multiple Imputation
MICE	Multiple Imputation using Chained Equations
MNAR	Missing not at random
QoL	Quality of Life
SDV	Source Data Verification
SF-36v2 [®]	Short-Form 36 version 2
TMG	Trial Management Group
TSC	Trial Steering Committee

9 Approval of Analysis Plan

Clinical Trials Research Unit (CTRU)

The following analysis plan for the ROLARR study has been approved by the following personnel. Any signed amendments to the plan will be filed with this document.

Trial Statistician: _____

Date: _____

Supervising Statistician: _____

Date: _____

Senior Trial Co-ordinator: _____

Date: _____

CTRU Principal Investigator: _____

Date: _____

Chief Investigator: _____

Date: _____

Additional information:

--

ROLARR Statistical Analysis Plan: Summary of Changes

Version & Date	Summary of Changes
Feb 2010	<p>n/a- Original protocol submitted for ethical review</p> <p>The original protocol outlines the endpoints to be analysed, their definitions (section 11 – Endpoints) as well as the planned methods of analysis (section 13 – Statistical Analysis). The first SAP expands on this substantially, but essentially the original plan for the analysis can be seen in the original protocol. Given this, we have listed the original protocol here and will summarise any changes between this and version 1 of the SAP, as well as summarising changes between version 1 and the final (version 2) SAP.</p>
V1.0 dated Jan 2015	<p>Changes from the original analysis plan as outlined in version 1.0 of the trial protocol:</p> <ul style="list-style-type: none"> • The use of the GOALS measure of intra-operative laparoscopic skills to independently grade ROLARR operating surgeons was removed (see details of protocol amendment for version 5.0 of the protocol) • The analysis by “actual surgery received” is described originally as a 3-arm analysis (laparoscopic, robotic and open). In addition to this, version 1.0 of the SAP describes a 2-arm “actual surgery received” (laparoscopic, robotic), since this may be of interest and in particular unlike the 3-arm approach it allows for this analysis by actual surgery received to be performed on the primary endpoint. • Length of learning originally planned to be incorporated as a level 2 covariate. This was amended such that the operating surgeon’s prior experience was incorporated as a level 1 covariate as per Cook et al (2004 – reference in the SAP) • An additional analysis to assess the learning effects by analysing only surgeons who had a lower than average conversion rate was dropped, since it was decided that the learning effects can be adequately described by the model proposed in the SAP without analysing a subset of the surgeons in this way. <p>In addition to these changes, the SAP outlines the plans for analysis in much more detail than the original protocol. For example, it gives much more detail about how missing data will be handled and the sensitivity analyses and subgroup analyses to be performed.</p>
V2.0 dated Feb 2015	<ul style="list-style-type: none"> • Additional information in section 2.3.2 about how any heterogeneity of timings of the quality of life measures will be addressed in the analysis. • Consideration given to the non-standard circumstance of a patient whose disease is determined to be benign after randomisation (section 2.3.5) • Stipulation that if a local pathology data item is missing then the corresponding central pathology data will be used in its place was removed due to unavailability of central pathology data. • Specification that each analysis will be a complete case analysis, with sensitivity analyses performed to investigate the potential impact of not incorporating patients with missing data, and details of how those patients will be incorporated if it is determined to be necessary. • Details added about sensitivity analyses relating to the central pathology review.