Supplementary Online Content


Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.
ALaCaRT: Australasian Laparoscopic Cancer of the Rectum Trial
A phase III prospective randomised trial comparing laparoscopic-assisted resection versus open resection for rectal cancer

Australasian Gastro-Intestinal Trials Group (AGITG)
Protocol number: AG0109CS
Version 5.0 30 May 2014

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New Zealand.

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REDACTED VERSION
A La CaRT: Australasian Laparoscopic Cancer of the Rectum Trial: A phase III prospective randomised trial comparing laparoscopic-assisted resection versus open resection for rectal cancer

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MRI – magnetic resonance imaging
## 1. SYNOPSIS

### TITLE
A La CaRT: A phase III prospective randomised trial comparing laparoscopic-assisted resection versus open resection for rectal cancer

### SPONSOR
AGITG (Investigator initiated)

### INDICATION
Primary rectal cancer

### OBJECTIVES

**Primary Objective:** To determine whether laparoscopic-assisted resection is not inferior to open rectal resection as a safe, effective oncologic approach to rectal cancer

**Secondary Objective:** To determine whether laparoscopic resection for rectal cancer is not inferior to open resection from a patient related benefit perspective, based on morbidity, mortality associated with surgery, disease-free survival and disease recurrence, quality of life, cost effectiveness and MRI staging accuracy.

### TRIAL DESIGN
Randomised phase III surgical study

### NUMBER OF PATIENTS
Total 470 patients

### TARGET POPULATION
Consenting male and female patients aged ≥ 18 years old with Stage T1-3 N0-2 M0-1 Primary Rectal Cancer

### TREATMENTS:
Arm A: Open laparotomy and resection for rectal cancer  
Arm B: Laparoscopic-assisted resection for rectal cancer

### ENDPOINTS:
**Primary endpoint:** A composite of oncologic parameters must be achieved for surgical resection to be successful.

- Circumferential margin ≥ 1mm
- Distal resected margin ≥ 1mm Completeness of total mesorectal excision (TME)

**Secondary endpoints**
- Morbidity/mortality associated with surgical intervention of the primary tumour
- Disease free survival and local pelvic recurrence at two years
- Overall survival at 5 years
- Quality of life (sexual function, bowel and bladder function and recovery parameters) up to 1 year
- Cost Effectiveness

**Tertiary endpoints**
- Disease staging by MRI

### STATISTICAL ANALYSES
Using an overall 95% confidence level, the current study and statistical analysis plan is designed for 80% power with 235 patients per arm required to detect 8% non-inferiority margin based on a 4 year planned accrual and 5 year follow up.
2. STUDY SCHEMA

Rectal cancer
Stage \(T_{1-3}, N_{0-2}, M_{0-1}\)

Stratify
- Site of 1° tumour (high, middle, low)
- Registering surgeon
- Planned operative procedure: low anterior resection or abdominoperineal resection
  - BMI <30 vs >30
  - Pre-operative radiotherapy
  - Metastases – \(M_0\) or \(M_1\)

Randomisation

Arm A
Open laparotomy and rectal resection

Arm B
Laparoscopic-assisted rectal resection
3. BACKGROUND INFORMATION

Rectal cancer is a major public health concern, particularly in countries such as Australia and New Zealand where the incidence is amongst the highest in the world. Although the mortality from rectal cancer has trended downwards over the past three decades, this still remains relatively high. With advances in surgery, chemotherapy, radiation therapy and earlier detection, the overall 5 year survival for rectal cancer has increased from 48% in 1985 to 65% in 2005.

Since the introduction of laparoscopic-assisted resection for colon cancer, there has been mounting enthusiasm for applying this technique to rectal cancer. Proponents of the laparoscopic technique assert that the same cancer resection can be achieved with minimal access surgery and that this technique is associated with improved short term outcomes.

However, the laparoscopic technique for the resection of rectal cancer cannot go forward without solid Level I evidence which establishes its safety and equivalence to the standard open operative procedure.

Surgical resection is the most important treatment modality for rectal cancer in terms of a curative resection, staging, prognosis and subsequent therapeutic decisions.

Additionally, the surgical integrity and pathologic staging of the resection is the most important prognostic factor in recurrent rectal cancer. The current standard of treatment for rectal cancer involves open laparotomy and resection of the involved bowel, an intact mesorectal fascial envelope and the accompanying lymph node tissue. Laparoscopic-assisted resection of rectal cancer must achieve at least equivalent results in comparison with open laparotomy prior to becoming an established means of resection.

Surgeons apply different surgical techniques to eradicate rectal cancer depending on the level of the cancer in the rectum and the oncologic distance necessary to obtain negative surgical margins. Abdominoperineal resection (APR) for low rectal cancers and low anterior resections for high rectal cancers are techniques which resect rectal cancer and establish adequate margins. The most appropriate and safe procedure for middle rectal cancer has not been adequately established.

A clinical trial is required to standardize laparoscopic-assisted resection by stage of disease and the anatomic position of the rectal cancer, and to assess the ability of the technique to produce adequate circumferential and distal margins, and complete total mesorectal excision (TME).

Studies have shown that surgical technique and the adequacy of resection predicts local recurrence rates in open rectal surgery and the quality of surgical technique and resection should be as relevant in laparoscopic rectal resection\(^{1,2}\). Recently published results support non-inferior short term outcomes in open and laparoscopic-assisted surgical resections for colon cancer with regards to the quality of the resection and recurrence rates. Similar findings may be revealed in rectal cancer, but technique, oncologic outcomes and recurrence patterns must first be systematically evaluated.

Quality of life after resection of rectal cancer has not been adequately studied. A recent Cochrane Collaboration Review\(^{3}\) found that there is no data available to compare laparoscopic and open laparotomy for rectal cancer and called for randomised control trials with Quality of Life Evaluation. Another Cochrane Review\(^{4}\) confirmed that a meta-analysis was not possible to compare sphincter sparing and abdominoperineal resection of rectal cancer. Once again, randomised data is needed. There have been several prospective reports of Quality of Life Evaluations after resection of rectal cancer that suggest age,
temporary and permanent stoma, ultra-low anterior resection, neoadjuvant therapy, colonic J-pouch reconstruction and gender may influence the quality of life to differing degrees over time in the domains of sexual function, bowel and bladder function and global health related quality of life.\textsuperscript{5-23} There are several instruments available which are validated questionnaires that focus on cancer- European Organisation for Research in the Treatment of Cancer and colorectal issues (EORTC-QLQ CR-29).

When evaluating quality of life after resection of rectal cancer the population must be as uniform as possible in order to limit the confounding factors which may bias the outcomes. In order to compare two methods of surgical treatment such as laparoscopic resection and open laparotomy this is especially critical. Therefore, covariates such as presence of an ileostomy or colostomy, neoadjuvant therapy, disease stage, age and gender become very important for the analysis. Timing of quality of life assessment also seems to influence the comparison of factors such as bowel function, sexual function and global health. Early comparison may show no difference in sexual function, but as time progresses there may develop real improvement in patients with sphincter sparing procedures but not in patients after APR.\textsuperscript{22} Sexual dysfunction may also be adversely affected over time as bowel function worsens.\textsuperscript{15} Global quality of life is adversely affected by worsening sexual function and pain after APR and data suggest that multiple quality of life instruments evaluating sexual, bowel, urologic and global areas need to be used in a homogeneous population at multiple time points in the setting of randomised trials.

There has been a fundamental shift in the treatment of rectal cancer. Laparotomy and total mesorectal excision are currently the standard of care. Local excision, minimally invasive techniques and sphincter-sparing operations have created a new and broader spectrum of care for rectal cancer patients. In the future, the partnership of molecular markers and minimally invasive techniques will further shape treatment options. The development of safe laparoscopic approaches to the treatment of rectal cancer will be the key to bringing the benefits of these new modalities to rectal cancer patients.

The primary focus of this randomised trial will be to determine whether laparoscopic-assisted resection of rectal cancer is non-inferior in safety and efficacy to the open technique of total mesorectal excision. The study will determine whether laparoscopic rectal resection can provide comparable cancer outcomes and favorably impact the short term outcomes of recovery.

**3.1 Epidemiology**

Colorectal cancer is the third most frequent malignancy in males, after prostate and lung cancer, and the second most frequent malignancy in females, after breast cancer. Rectal cancer is a major public health concern, particularly in countries such as Australia and New Zealand where the incidence is amongst the highest in the world (~4000 new cases per year).

**3.2 Therapy with Neoadjuvant Chemoradiotherapy**

In patients with Stage III rectal cancer, chemoradiotherapy given prior to definitive surgery has been shown to significantly decrease local recurrence. Various trials have demonstrated a ~50% reduction in local recurrence from 25% down to 12% or lower. Whether the best pre-operative treatment is a short course of radiation treatment (5 days) or 5-6 weeks of chemoradiotherapy is the subject of a recently completed Australasian trial conducted by the Trans-Tasman Radiation Oncology Group (TROG) and the AGITG. Results\textsuperscript{24} show there was no clear evidence for a difference between short course and long course in terms of local recurrence at 3 years. In addition distant recurrence and overall survival rates were similar. Ngan et al. found that both short course and long course radiotherapy provided good local control. Late toxicity rates were not
substantially different. Results at this stage do not include longer term follow-up of outcomes, including quality of life.

### 3.3 MRI Staging of Rectal Cancer

Pelvic MRI is deemed the most appropriate pre-operative imaging modality for rectal cancer. The use of MRI prior to surgical removal of rectal cancer has been shown to provide definition of anatomy important to the performance of rectal cancer surgery\(^25\). In particular the mesorectal fascia may be defined and this provides important information for staging of tumors, assessing resectability, planning surgery, and selecting patients for preoperative neoadjuvant therapy\(^26\). High-spatial-resolution MRI has been shown to depict a number of structures of importance in total mesorectal excision surgery.

### 3.4 Surgery

Adequate resection of colorectal cancers is the principal curative treatment. About 75% of all rectal cancer patients can be treated by surgery with curative intent, of which 10% are cured by local excision. In about 25% patients, extensive surgery is not an option because of poor performance or advanced stage of cancer at the time of presentation. The limited workspace in the lower pelvis and the bony structures surrounding it make it difficult to operate on the rectum and impede complete resection of rectal cancer. Until the late 70’s a blunt dissection was performed in which lateral excision was often incomplete with consequently high rates of local recurrence. However, a new procedure, total mesorectal excision, was advocated and promoted by Heald in 1982, which entails sharp dissection along anatomical planes resulting in more complete resection and consequent reduction in local recurrence, in addition to better preserving the presacral nerves and vessels resulting in better patient-reported outcomes.

### 3.5 Open Rectal Resection

Conventional surgery for rectal cancer requires extensive laparotomy usually with a long midline incision of 25-30cm (or longer). However, there is also a more recent practice of combining both laparoscopic and open surgery, often referred to as “hybrid” surgery. This allows the surgeon to laparoscopically perform the abdominal component of the operation i.e. mobilising the splenic flexure and dividing /securing the main blood vessels, but not laparoscopically doing the more difficult pelvic dissection. A lower midline or transverse incision can then be made to perform the pelvic dissection via a smaller laparotomy than would otherwise have been possible if the splenic flexure component had not been done laparoscopically.

### 3.6 Laparoscopy

Laparoscopic surgery appears to be associated with less operative trauma and blood loss than open surgery. These factors are considered beneficial for survival\(^27,28\).

### 3.7 Laparoscopic Surgery for Colon Cancer

There were early concerns about abdominal wall metastases\(^29\), however, recent results indicate that with good technique this is no longer a problem and several large multicentre trials have now demonstrated an equivalent survival outcome between open or laparoscopic surgery for the treatment of colon cancer\(^30,31\). In the US Clinical Outcomes of Surgical Therapy (COST) Study\(^31\) where 872 randomised patients have been followed for a median of 7 years (range 5-10 years), disease-free survival (open 74.6%, laparoscopic 76.4%, p=0.93) was similar for the 2 groups as were overall recurrence rates (open 21.8%, laparoscopic 19.4%, p=0.25). A similar study also funded by the NHMRC has been conducted in Australia and New Zealand (ALCCaS)\(^32\), and while
the short term-outcomes have been analysed and published, the results of the longer-term follow-up are still awaited.

Although most studies of laparoscopic-assisted colon resection exclude rectal cancer, there are several single institution studies which demonstrate the feasibility of laparoscopic-assisted resection of rectal cancer (LARR). Feliciotti et al prospectedly studied laparoscopic-assisted and open resections and found both methods were associated with similar surgical and long-term outcomes. One single site randomised controlled trial found laparoscopic resection had similar survival or disease control for patients with rectosigmoid cancer when compared with open surgery, albeit based on insufficient numbers.

The only published multicentre randomised trial in this area to date is from the United Kingdom Medical Research Council Conventional versus Laparoscopic Assisted Surgery in Colorectal Cancer (UKMRC CLASICC) Trial, which included 242 patients with rectal cancer of 794 patients enrolled from July 1, 1996, to June 28, 2002. Overall, the study results were encouraging, with similar short and long-term outcomes for both groups. However the study raised concerns regarding the technique. The overall conversion rate (from laparoscopic to an open procedure) was 29% (n=143 conversions) for the laparoscopic cohort; comprising a conversion rate of 34% (82/242) for the rectal tumours. Further, in the rectal surgery subgroup, the circumferential radial margin positivity was greater in the laparoscopic group when compared with open surgery. This difference was not appreciated in the abdominal-perineal laparoscopic procedure group. While this difference did not reach statistical significance, the trend toward a higher rate of tumours with positive margins with laparoscopic low anterior resection (LAR) (12% vs 6% difference 6% 95% CI -2 to 14%) calls for further systematic investigation. However, the subsequent study report found there was no difference in cure survival for patients undergoing anterior resection (AR) or abdominal perineal resection (APR) in either technique group (AR-open 66.7%, laparoscopic 74.6%; APR-open 57.7%, laparoscopic 65.2%). These findings held for the three year disease free analysis as well. There was no significant difference in three year local recurrence rates after AR of rectal cancer (7% open, 7.8% laparoscopic) or abdominoperineal resection of rectal cancer (21% open, 15% laparoscopic). There were no differences in quality of life parameters for colon or rectal cancer. In addition, an important limitation of this study was that there was no standardisation of the use of neoadjuvant chemoradiotherapy within the rectal cancer group, such that this trial does not mimic current standards.

3.8 Rationale for using Surgical Quality as the Primary Outcome

The quality of the surgical resection in addition to the resection margins have been demonstrated to be important factors associated with lower rates of local and distant recurrence and better overall survival. Most important prognostic determinants have been the completeness of the TME and the adequacy of the circumferential resection margin (CRM). In 2002 Nagtegaal and Quirke proposed 3 grades for completeness of TME, grade 1= incomplete, grade 2=almost complete, grade 3=complete, and reported an increased risk of local and distant recurrence among patients with grade 1 resections. This work was extended by Maslekar et al in a UK study of 130 patients with rectal cancer undergoing potentially curative surgery.

Completeness of excision of the mesorectum (grade) was an independent prognostic factor for both local and overall recurrence in a multivariate Cox regression analysis (as summarised in the following table).

<table>
<thead>
<tr>
<th>Completeness of TME</th>
<th>n (%)</th>
<th>Local recurrence</th>
<th>Overall Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>17 (13%)</td>
<td>41%</td>
<td>50%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>52 (40%)</td>
<td>5.7%</td>
<td>17%</td>
</tr>
</tbody>
</table>
With respect to CRM, in a Swedish population study of 686 patients who underwent TME with a known CRM following potentially curative resection and after a median follow-up of 29 (range 14-60) months, the overall local recurrence rate was 7 per cent (46 of 686 patients); 22 per cent among patients with a positive resection margin and 5 per cent in those with a negative margin (margin greater than 1 mm). Forty per cent of patients with a positive margin developed distant metastasis, compared with 12 per cent of those with a negative margin. With decreasing circumferential margin there was an exponential increase in the rates of local recurrence, metastasis and death. Further, in a Dutch study involving 1324 patients with rectal cancer, multivariate analysis identified nodal status (P = .001) and circumferential margin (P = .001) involvement as the most important prognostic factors for survival. And a recent review by Natgegaal and Quirke found that involvement of the CRM is a powerful predictor of both the development of distant metastases (HR=2.8; 95% CI, 1.9 to 4.3) and survival (HR= 1.7, 95% CI, 1.3 to 2.3).

The most recent study in support of the importance of the correct surgical plane of dissection has been the analysis of the CR-07 randomised trial for rectal cancer and radiotherapy. Patients in the pre-operative radiotherapy group who had a resection in the mesorectal (grade 3) plane had a 3-year local recurrence rate of only 1%. By comparison, the estimated local recurrence rates were 7% (5-11%) for intramesorectal (grade 2) and 13% (8-21%) for muscularis propria (grade 1) groups.

In addition, it has been found that the colorectal surgery experience of the surgeon is predictive of improved local recurrence. Further, for the laparoscopic procedure, the number of prior procedures significantly reduced the duration of the surgery (as seen in the COLOR study, p=0.03) and the number of conversions. In the CLASSIC study, the rate of conversions to open procedures decreased from 38% in year 1 to 16% in year 6.

3.9 Open studies

There are currently two international Phase III randomised studies of similar design to A La CaRT (as summarised in the following table).

<table>
<thead>
<tr>
<th>Feature</th>
<th>COLOR II</th>
<th>ACOSOG Z6051</th>
<th>A La CaRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison</td>
<td>Lap vs Open</td>
<td>Lap vs Open</td>
<td>Lap vs Open</td>
</tr>
<tr>
<td>Region</td>
<td>Europe</td>
<td>Nth America</td>
<td>ANZ</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Local recurrence (3 yrs)</td>
<td>Surgical path success</td>
<td>Surgical path success</td>
</tr>
<tr>
<td>Planned Size</td>
<td>1275</td>
<td>480</td>
<td>470</td>
</tr>
<tr>
<td>Progress</td>
<td>Opened June 2003</td>
<td>Opened August 2008</td>
<td>Opened March 2010</td>
</tr>
</tbody>
</table>

Table 2. Design features of Color II, ACOSOG Z6051 and A La CaRT studies.

Each trial will provide useful information on short and long-term clinical outcomes. There is a formal agreement to prospectively combine the results of Z6051 and A La CaRT to assess recurrence rates and linkage of these outcomes to surgical success. In addition it is proposed to undertake a meta-analysis of all 3 trials on long term survival.
4. TRIAL OBJECTIVES

4.1 Primary Objective
To determine whether laparoscopic-assisted resection is not inferior to open rectal resection as a safe, effective oncologic approach to rectal cancer.

4.2 Secondary Objectives
To determine whether laparoscopic resection for rectal cancer is not inferior to open resection from a patient related benefit perspective, based on morbidity, mortality associated with surgery, disease-free survival and disease recurrence, quality of life, cost effectiveness and MRI staging accuracy.

5. TRIAL DESIGN

5.1 Design
This is a randomised phase III trial evaluating the safety and efficacy of laparoscopic resection for rectal cancer. The study is expected to randomise 470 patients from approximately 20 sites in Australia and New Zealand. Patients will be randomised to either open laparotomy and rectal resection or laparoscopic-assisted rectal resection.

5.2 Randomisation
Randomisation will be performed centrally at the NHMRC Clinical Trials Centre/AGITG Coordinating Centre. Upon confirmation of eligibility patients will be stratified by site of primary tumour (high, middle or low rectum), registering surgeon, planned operative procedure (low anterior resection or abdominoperineal resection), body mass index (BMI) <30 or ≥30, pre-operative radiotherapy and metastatic disease. Patients will be randomised 1:1 to either open laparotomy and rectal resection or laparoscopic-assisted rectal resection.

No waivers or exemptions to any eligibility criteria are permitted. All eligibility criteria must be fully documented in the patient’s medical notes.

The NHMRC Clinical Trials Centre/AGITG Coordinating Centre will validate all investigator and site credentials prior to randomisation. Once randomisation is completed, a unique A La CaRT patient ID number and treatment assignment will be generated and provided to the site.

5.3 Endpoints
The primary endpoint will be a composite endpoint of oncologic factors which are indicative of an adequate surgical resection based on pathologic evaluation.

Primary endpoint oncologic parameters
- Circumferential margin ≥ 1mm.
- Distal resected margin ≥ 1mm Completeness of TME (A complete TME is defined as a rectal resection specimen which has an intact mesorectum and covering peritoneal envelope all the way to the level of rectal transaction with no coning in of the mesorectum above the point of transection. The surface of the peritoneal covering should be smooth and shiny with no defects exposing the underlying fat.)
Secondary endpoint parameters

- Morbidity/mortality associated with surgical intervention of the primary tumour (length of stay, death within 30 days, return to theatre within thirty days, septic complications, anastomotic leak, abscess formation, significant bleeding, primary or secondary ileus, urinary retention, problems with healing, function, management of ostomy).
- Disease free survival and local pelvic recurrence at two years
- Overall survival at five years.
- Quality of life (sexual function, bowel and bladder function and recovery parameters) up to 1 year.
- Cost-effectiveness, both within the trial period and extrapolated to long term outcomes
- Disease staging by MRI

6. SUBJECT POPULATION

6.1 Subject Population

The target population for this trial are consenting male and female patients aged ≥18 years with primary rectal cancer Stage T1-3, N0-2, M0-1.

Observed incidence of rectal cancer suggests a slightly higher incidence of rectal cancer in males (58% of all rectal cancer patients) compared to females (42% of all rectal cancer patients). Therefore, we anticipate fewer female patients than male patients in the trial.

To participate in this study, patients must meet all of the inclusion criteria and have none of the exclusion criteria. No waivers on these criteria will be granted.

6.2 Inclusion criteria

a. Histological diagnosis of adenocarcinoma of the rectum (<15cm from the anal verge as measured by rigid sigmoidoscopy).

b. T1-3 N0 M0, T1-3 N1 M0 or T1-3 N0-2 M1 disease as determined by pre-treatment CT scans and pelvic MRI (or endorectal ultrasound if MRI contraindicated or if tumour is ≥10cm from anal verge))
   i. For evaluation of pelvis: MRI +/- ERUS; or ERUS alone if MRI contraindicated or if tumour is ≥10cm from anal verge
   ii. For evaluation of abdomen, liver: CT
   iii. For evaluation of chest: either CT or CXR

c. Age ≥ 18 years.
d. ECOG Performance Status: 0, 1 or 2.
e. Written informed consent.
f. Life expectancy of at least 12 weeks.

6.3 Exclusion criteria

a. Medical or psychiatric conditions that compromise the patient’s ability to give informed consent or comply with the study protocol.
b. Pregnancy or breast feeding.
c. Any uncontrolled concurrent medical condition.
d. Any co-morbid disease that would increase risk of morbidity.
e. Evidence of T4 disease extending to circumferential margin of rectum or invading adjacent organs.
f. Evidence of systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude surgery, or other severe incapacitating disease, i.e. ASA IV (a patient with severe systemic disease that is a constant threat to life) or ASA V (a moribund patient who is not expected to survive without the operation).

g. History of conditions that would preclude use of a laparoscopic approach (e.g. multiple previous major laparotomies, severe adhesions).

h. Concurrent or previous invasive pelvic malignancy (cervical, uterine and rectal) within five years prior to registration.

6.4 Withdrawal by patient
Patients who are randomised but refuse surgery will be followed up. These patients would be encouraged to allow collection of their vital status through clinic records for overall survival data.

6.5 Concurrent participation in other clinical trials
Consideration will be given to patients participating in other clinical trials on a case by case basis.

7. QUALITY ASSURANCE AND CONTROL

7.1 Surgeons’ Credentialing

7.1.1 Surgeon Skill Verification
Surgeons must be proficient at the proper open technique for total mesorectal excision for rectal cancer. Surgeon credentialing in BOTH laparoscopic colon and laparoscopic rectal surgery will be required for participation in this study.

7.1.2 Laparoscopic Colon Credentialing
Surgeons will be credentialed for laparoscopic colon surgery, having performed at least 100 laparoscopic, laparoscopically-assisted or hand-assisted colon operations. Operative and pathology reports will be submitted for the last 20 laparoscopic colon resections. ALCCaS trial participation will substitute for this credentialing.

7.1.3 Laparoscopic Rectal Credentialing
Surgeons will be credentialed for laparoscopic rectal surgery, having performed at least 30 laparoscopic, laparoscopically-assisted or hand-assisted rectal operations. Surgeons will provide operative reports and pathology reports for these 30 rectal cases and an unedited DVD of their laparoscopic rectal technique. All DVDs submitted for this trial will be reviewed by two designated investigators and approved for oncologic technique and practice.

7.2 Surgeons’ Assessment Criteria
Criteria to be assessed include:

- Male pelvic dissection
- Splenic flexure mobilisation
- High ligation Inferior Mesenteric Vein (IMV) at level of duodenum or more proximal
- High ligation Inferior Mesenteric Artery (IMA) - proximal to left colic vessel
- Left ureter identification
- Hypogastric nerve preservation at pelvic brim
- Identification of Denonvilliers fascia
- Intact total mesorectal excision
- Dissection in mesorectal plane
Dissection down to bare muscular rectal tube

7.3 Submission Information

Complete operative reports, pathology reports, DVD/video documentation and a completed surgical assessment submission form must be submitted to:

A La CaRT Trial Coordinator
NHMRC CTC
Locked Bag 77
Camperdown NSW 1450

No registration will be accepted until skills verification and all credentialing requirements are completed, received and approved by the Study Chair or designee. In submitting these materials for assessment surgeons will be agreeing to comply with study guidelines. Surgeons who fail to meet the criteria will be informed by the Study Chair or his/her designee and will be given the opportunity to respond to the evaluation within ten days.

7.4 Performance Monitoring

7.4.1 Study Chair Review
The Study Chair or designee will review at least one patient randomly selected per site to confirm patient eligibility and intervention compliance. If an investigator has a possible performance issue, the Study Chair or designee will review the issue(s) and make recommendations to the investigator. It is expected that in most cases, the Study Chair or designee will work with the investigator to improve performance. However, the Study Chair or designee is empowered to suspend protocol participation, if necessary. (See Appendix 7)

7.4.2 Monitoring of Surgical Performance
Video audit of laparoscopic procedures will take place throughout the trial, with random assessment of 20% of submitted videos after accrual of 50, 150, 250 and 350. Therefore all laparoscopic procedures must be filmed and confirmed as having been filmed on the appropriate case report form. Failure to film procedures will be noted by the Study Chair and reported to the Trial Management Committee (TMC). The Study Chair or designee and TMC is empowered to suspend protocol participation if necessary until appropriate facilities to film laparoscopic procedures are in place. Sites will be contacted when patient cases have been selected for review. Details of required review materials and submission instructions will be provided. Annual site visits will be performed by the Pathology Review Committee to assess surgical technique and quality of pathology assessment. (See Appendix 7)

7.4.3 Registering Surgeon
The investigator intending to register a patient to this study must be either a member of the Colorectal Surgical Society of Australia and New Zealand (CSSANZ), nominated by a member of CSSANZ, or endorsed by another cooperative group such as American College of Surgeons Oncology Group (ACOSOG), Eastern Co-operative Oncology Group (ECOG), South West Oncology Group (SWOG), Cancer and Leukaemia Group B (CALGB) or equivalent.
8. TREATMENT OF PATIENTS

8.1 Patient Treatment Arms

8.1.1 Arm A: Open Laparotomy and Rectal Resection
This may include hybrid operations i.e. laparoscopic or hand-assisted mobilisation of the left colon with division of inferior mesenteric vessels. However, the rectal mobilisation is to be performed via a laparotomy incision.

8.1.2 Arm B: Laparoscopic-assisted Rectal Resection
Transection of the anorectal junction can be achieved either with endoscopic staplers or using transverse staplers via the specimen-extraction site.

8.2 Conversion
Conversion will be defined as a change in operative approach to otherwise achieve the final goal; i.e. laparoscopic-assisted technique to a hybrid procedure, or any conversion to an open procedure. Conversion to a laparotomy will be at the discretion of the individual surgeon for concerns of patient safety, technical difficulties, inability to complete the planned procedure for sphincter sparing or associated conditions requiring treatment. Conversion will be defined as a fascial incision which is longer than 10 cm, utilized to achieve anything other than specimen extraction. (Largest handport size is \( \approx 8 \) cm). Utilizing the extraction site for transverse stapler insertion to accomplish the distal anastomosis will not be considered a conversion.

Identification of any grossly visible positive margins or extensions into adjacent organs will mandate conversion to an open procedure. Completion of the pelvic dissection through the extraction site also will be considered conversion.

8.3 Chemoradiotherapy: Pre and Post-surgery
If no neoadjuvant chemotherapy or radiotherapy was received, surgery can be performed up to 8 weeks post-randomisation.

8.3.1 Neoadjuvant Chemoradiation Therapy
Patients eligible for this trial with either T3 or N1-2 tumours will typically have completed 5 fluorouracil (5FU)-based neoadjuvant chemotherapy/radiation therapy per the institution’s individual policy. Not all patients with T3 tumours will require neo-adjuvant treatment. A selective approach to the neo-adjuvant treatment should reflect current indications and surgeon/patient preferences for that institution.

Capecitabine may be substituted for 5FU at the investigator’s discretion.

9.3.1.1 Short course Radiotherapy
Short Course Radiotherapy may also be used prior to surgery.

The time left between the completion of neoadjuvant therapy and surgery is at the operating surgeon’s discretion.

8.3.2 Post-operative Adjuvant Therapy
Patients will be evaluated after surgery to determine the need for subsequent care based on the final pathology. All patients should be instructed to notify the operating surgeon of any additional...
therapy the patient will receive. Patients should not start treatment on any other investigational trial involving intervention or invasive diagnostic procedures ≤ 30 days following surgery to enable a complete evaluation of post-operative adverse events and complications occurring within 30 days of surgery. Data on the use of radiotherapy post-operatively will be collected.

8.4 Pre-operative Evaluation

Patients will be seen for the preoperative evaluation within 6-8 weeks prior to surgery. Tests and evaluations should be conducted as required by the Study Calendar.

8.5 Surgery

8.5.1 Pre-operative Care

Patients will be admitted to hospital on the morning of surgery or the day prior to surgery for complicating medical conditions (as per the surgeon's discretion).

All patients will receive bowel prep per institutional colorectal standard routine.

The site of the ileostomy/colostomy (potential or planned) will be marked preoperatively as per institutional standard routine.

8.5.2 Intra-operative Procedures

Anaesthetic care will include general endotracheal anaesthesia with gastric and bladder decompression.

Extent of colon and rectal resection will be determined by the site of the tumour on preoperative exam. The manner of anastomosis (stapled or hand sewn) will be based on the surgeon's preference. Extent of resection will be documented for all procedures in the operative report and on case report forms (CRFs).

8.5.3 Intra-operative Pathology

Surgeons will measure fresh, unstretched proximal and distal margins in the operating room. The completeness of the TME resection will be evaluated by the pathologist in the operating room when possible. Prior to opening the specimen, it should be prepared by the pathologist to evaluate radial margins by applying ink to the mesorectal surface in the area of the tumour. The mesorectal specimen should be photographed with a digital camera to verify the quality of the dissection. Standardisation of photography will need to be agreed on and adhered to at each site (e.g. at 20 cm, macro mode, no flash, etc.).

8.5.4 Documentation of Operative procedures and Findings

Operative procedures and findings will be documented in the institutional operative and pathology reports and on required case report forms. Laparoscopic procedures will be recorded beginning at pelvic dissection, (in digital format saved to DVD or hard drive) and stored at sites. They will be provided to the NHMRC CTC on request for random audit requirements. (See Appendix 7)

8.5.5 Post-operative Care

Post-operative care will be according to current standards as directed by the operative surgeon. However, in order to provide a degree of Standardisation:

- Pain control will be provided using parenteral (intravenous) patient controlled administration (PCA) of narcotics or analgesics.
- Oral analgesics will be offered prn when the patient has resumed oral intake.
- Narcotic/analgesic use will be monitored and recorded for study purposes.
- The initiation of oral intake and dietary advances will be made according to individual patient tolerance.
• The day of first postoperative flatus and bowel movements will be monitored and recorded.
• Intravenous fluids will consist of maintenance crystalloid solution in addition to blood products as needed until the patient is able to sustain oral intake.
• Hospital discharge will occur only after the patient has shown diet tolerance, return of bowel function and able to resume self-care with minimal assistance.

8.6 Patient Follow-up
Post-operative follow up will include a visit in the hospital stay at day three, then at day 14, four to six weeks, 3 months, 6 months, 9 months, 12 months, 18 months and 24 months after discharge.

Further long-term follow-up will be conducted annually for an additional three (3) years after the 24 months follow up visit. This will allow a total of five (5) years follow up. Follow-up may be conducted through the patient’s local physician (for patients in remote centres), per surgeon discretion.

Type and severity of activity restrictions will be documented on the Quality of Life forms.

Participation in this study is voluntary; patients will be able to withdraw at any time. If a patient decides to refuse the study treatment they should be encouraged to continue to allow their health status to be reviewed via continued study visits or as detailed in their medical records.

8.6.1 Follow-up of Patients with Disease Relapse
If disease relapse is diagnosed, required data forms will be submitted to document the relapse. Patients with recurrent disease will be followed for survival every 6 months for 5 years.

8.6.2 Follow-up of Patients who receive Opposite Surgery
Patients who are randomised but receive the opposite surgery from their randomised arm (e.g. patient receives laparoscopic surgery after randomisation to the open surgery arm) will be followed as detailed in this protocol for 5 years.

8.6.3 Follow-up of Patients who Refuse Surgery
Patients who are randomised but refuse all surgery will be followed for inclusion in intention to treat analysis. These patients should be encouraged to allow the collection of their health status through their clinical notes.

9. EFFICACY AND SAFETY

9.1 Assessment of Efficacy

9.1.1 Specification of the Efficacy parameters
Evaluation at the time of surgery will include:
• Intact TME resection
• Circumferential and distal margin positivity
• Lymph node harvest and number of positive lymph nodes
• Evaluation of surgical complications

9.2 Pathologic Evaluation of the Resected Specimen
The resected specimen must be inspected fresh in the pathology department or operating room of each participating institution. Whenever possible, the pathologist should not be informed of the patient’s treatment assignment.
9.2.1 Macroscopic Judgement of the Resected Specimen
The quality of the mesorectal excision will be categorized as 3) complete; 2) nearly complete; or 1) incomplete; according to Dutch Colorectal Cancer Group methods.32

- Grade 3: Complete: intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm, and there is no coning toward the distal margin of the specimen. There is a smooth circumferential resection margin on slicing.
- Grade 2: Nearly complete: moderate bulk to the mesorectum, but irregularity of the mesorectal surface. Moderate coning of the specimen is allowed. At no site is the muscularis propria visible, with the exception of the insertion of the levator muscles.
- Grade 1: Incomplete: little bulk to mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin.

9.2.2 Preparation of Specimen
- The distal margin should be measured both fresh in theatre, and by the pathologist after delivery.
- The specimen, pinned by the surgeon in the operating room for orientation, will be inked by the pathologist for margin determination, and fixed in 10% formalin.
- The size of the residual tumour or ulcer corresponding to the tumour site will be measured.
- Dissection of the fixed specimen will consist of serial slicing of the rectal wall through the tumour and surrounding mesorectal fat in a plane perpendicular to the mucosa.
- A careful search will be conducted for any potential lymph nodes in the fragment of fat contained in the specimen.
- Sections will be obtained at 5 mm intervals, embedded in paraffin, cut in 5 µm sections, and stained with haematoxilyn and eosin (H&E).
- The deepest level of invasion in the rectal wall or mesorectal tissue will be determined and the distance measured from the overlying inked surface to the tumour.
- Any lymph nodes will be cut in half longitudinally; the half of the node not used for diagnostic purposes will be fixed in formalin and embedded in paraffin.
- Findings will be reported per the recommendations of the Association of Directors of Anatomic and Surgical Pathology [Pathology 1996].39

9.2.3 Pathology Review Committee
A Pathology Review Committee (PRC) will provide a random audit of 1 in 5 pathologic case report forms, pathology reports and TME video images of the specimen. The PRC will standardize the use of inking the mesenteric surface at the level of the tumour to determine the closest point of tumour invasion to the inked surface. The PRC will evaluate the reports and provide education for failure to meet minimal standards of the pathology evaluation with potential site closure if minimal standards cannot be met. The parameters to be included in the reports are:

- Distal margin of the unstretched fresh specimen
- Proximal margins of the unstretched fresh specimen
- Circumferential radial margin
- Completeness of TME specimen
- Number of lymph nodes in mesentery and number positive

Sites will be contacted when patient cases have been selected for review. Required review materials and submission instructions will be provided. (See Appendix 7)
9.2.4 Evaluation of Disease Recurrence

The appearance of rectal carcinoma in the primary site, nodal basin or distant organ sites during follow-up will be classified as recurrent cancer. Recurrence will be classified as local or distant. Suspected tumour recurrence within the surgical field should be documented histologically or cytologically.

Pathological documentation of suspected distant metastasis is also recommended.

Appropriate imaging should be used to document extent of disease (PET/CT, CT, MRI).

9.3 Assessment of Safety

9.3.1 Data Safety and Monitoring

Patient data will be monitored by the Australasian Gastro-Intestinal Trials Group (AGITG) Independent Data Monitoring Committee (IDMC) for significant adverse effects on cancer outcomes, safety and feasibility.

In addition, the following rates are based on the current literature review and are provided to the IDMC as guidelines for monitoring of additional safety related endpoints.

- Rate of conversion greater than 20%.
- Rate of anastomotic leak greater than a 6% increase compared to open procedure.
- Rate of positive circumferential margins greater than a 6% increase compared to open procedure.
- Surgical mortality greater than 5%.
- Rate of rectal perforation greater than a 6% increase compared to open procedure.

9.3.2 Accrual Rate and Feasibility

Accrual rate and feasibility shall also be assessed. As described in section 11, Statistical Considerations, there will be a specific futility monitoring plan for the primary endpoint.

9.3.3 Adverse Events and Serious Adverse Events

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

In this study we are recording AEs that occur in a patient who has undergone surgical resection of primary rectal cancer as per this protocol.

An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with surgical resection of primary rectal cancer, whether or not considered related to the surgical procedure. An adverse event is any adverse change (developing or worsening) from the patient’s pre-treatment condition, including intercurrent illness.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that:
- results in death
- is life-threatening (i.e. the subject is at risk of death at the time of the event
- requires inpatient hospitalisation or prolongation of existing hospitalisation or
- results in persistent or significant disability or incapacity

NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Important medical events which may not be immediately life-threatening or result in death or hospitalisation but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

Hospitalisations or deaths related to disease progression will not be reported as SAEs.

### 9.4 Adverse Event Reporting

Adverse events must be described and graded using the terminology and grading categories defined in the most current version of the NCI’s Common Terminology Criteria (CTCAE) version 3.0. [See Appendix 1] All adverse events, regardless of grade or treatment attribution, must be recorded on AE case report forms (CRFs). Attribution to protocol intervention for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

#### 9.4.1 Monitoring of Patients with Adverse Events

Any AE that occurs in the course of this study must be monitored and followed up until 30 days after the date of surgery. In addition SAEs must be reported via an SAE report form (Please refer to section 10.5. Procedure for Reporting Serious Adverse Events).

It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

Expected adverse events are summarised in the table below.

<table>
<thead>
<tr>
<th>Peri-operative</th>
<th>Complications</th>
<th>Laparoscopic rectal resection</th>
<th>Open rectal resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0-2%</td>
<td>0-7.4%</td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>20%</td>
<td>1-17%</td>
<td></td>
</tr>
<tr>
<td>Perineal wound infection</td>
<td>24%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Abdominal wound infection</td>
<td>0-3.4%</td>
<td>3-24%</td>
<td></td>
</tr>
<tr>
<td>Stomal complications</td>
<td>4-10%</td>
<td>4-10%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-operative</th>
<th>More frequent</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage/Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistula</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethral injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection/Abscess</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stricture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal Perforation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stoma complications
- Thrombosis/Embolism
- Infection/Lung (Pneumonia)
- Cardiac Ischaemia/Infarction (myocardial infarction)
- Ileus
- Hernia

**Less Frequent**
- Sexual dysfunction

**Late or Delayed Complications >30 days after surgery**
- Bowel obstruction
- Incisional hernia (with or without repair)

**Hospital admission**
Details of hospital admissions will be recorded in the appropriate CRF, including dates, location, and admitting surgeon’s name. The “reason for admission” will provide guidance as to whether the hospitalisation was related to the cancer diagnosis and surgery or for other reasons.

### Table 3. Expected Adverse Events

**9.5 Schedule of Assessments**
A schedule of assessments is summarised below in the study calendar.

T₁-3 N₀ M₀, T₁-3 N₁ M₀ or T₁-3 N₀₂ M₁ disease as determined by pre-treatment CT scans and pelvic MRI (or endorectal ultrasound if MRI contraindicated or ≥10cm from anal verge)

iv. For evaluation of pelvis: MRI +/- ERUS; or ERUS alone if MRI contraindicated or ≥10cm from anal verge

v. For evaluation of abdomen, liver: CT

vi. For evaluation of chest: either CT or CXR
Table 4. Study Calendar

*Between 3 years and 5 years, CEA, colonoscopy, chest x-ray and CT abdomen/pelvis are performed as per doctor’s discretion.

Visit windows:
- Informed consents must be signed within 28 days prior to randomisation.
- Pre-randomisation assessments must be performed within 8 weeks prior to surgery.
- Pre-op lab tests and completion of questionnaires must be done between randomisation and surgery.
- 4-6 weeks assessments must be done within 4 to 6 weeks after surgery +/- 2 days.

9.6 Study Measurements

9.6.1 Morbidity and Mortality
Early, in hospital and late (within 30 days) morbidity and mortality will be closely monitored and recorded on the appropriate CRF using Common Terminology Criteria for Adverse Events v3.0 (CTCAE). (See Appendix 1)

- Infection
- Primary ileus
- Secondary ileus
- Urinary retention/dysfunction
- Peri-operative haemorrhage
- General medical complications
- Anaesthetic complications
- Stomal complications *
- Extended hospitalisation

* Post-operatively, early stomal complications may include stenosis, haemorrhage, infection, ischaemia, management difficulties; long term stomal complications may include prolapse, retraction or herniation and may require surgical revision. Complications of reversal of stoma may include anastomotic leak, haemorrhage, and wound infection.

9.6.2 Quality of Life (QOL)
The study will compare the impact of the two treatment arms on QOL.

The impact of the disease and surgery on patient function and quality of life will be evaluated at randomisation. Subsequent assessments will be collected post-operatively at day 3, day 14, then at four to six weeks, 3 months and 12 months. This assessment schedule will allow collection of data on short and long-term QOL-related deficits.

QOL will be assessed using the following European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires - CR-29 and PR-25. [See Appendix 3]

The EORTC QLQ-CR29 is specific for colorectal cancer and assesses disease symptoms, side effects of surgery, chemotherapy and radiotherapy, body image, sexuality, future perspective and includes 18 questions with another 8 or 9 questions completed as subsamples of patients (males or females and patients with or without a stoma). This will be completed at randomisation, day 3, day 14, then at four to six weeks, 3 months and 12 months.
The EORTC QLQ-PR-25 is specific for sexual and bladder function, and will be completed at randomisation and then at 4 weeks, 3 months and 12 months.

The International Prostate Symptom Score (IPSS) is specific for prostate symptoms and will be completed at randomisation and then at 4 weeks, 3 months and 12 months.

The Female Sexual Function Index (FSFI) and International Index of Erectile Function (IIEF) are specific for sexual function and will be completed at randomisation and then at 4 weeks, 3 months and 12 months.

9.6.3 Cost effectiveness

The inclusion of a health economics sub study is important as it is expected that the intervention will be significantly cost saving in the short term. There is a need to verify this hypothesis, as well as to model the costs and health outcomes that will occur beyond the trial's follow up period. The results of this study will further inform decision makers about the merits of the intervention.

The study will estimate the cost effectiveness of the surgical intervention for both short and long term outcomes. If the intervention is found to be non-inferior, a cost minimisation analysis will be performed using data collected within the trial to determine any direct cost savings associated with the intervention. A decision model will then be developed to extrapolate trial data and project long term costs and health outcomes. An incremental cost per quality adjusted life year (QALY) will be estimated from the modeled analysis.

The AQoL-8D questionnaire will provide the utility scores needed to calculate QALYs. The direct health care costs of the intervention will be estimated using trial data on hospitalisations and adverse events.

In addition, the Labour Force and Income Impacts of Illness questionnaire will measure labour force participation and income impacts of illness on patients and will be collected at baseline and at three follow up time points. This survey will be used to estimate the indirect costs associated with the treatments (i.e. the costs incurred by patients), allowing the study to determine the cost effectiveness of the intervention from a societal perspective.

9.6.4 MRI Staging

Patients’ who undergo MRI (mandatory except for those with a medical contraindication for MRI or if the tumour is ≥10cm from anal verge) will have their MRI examination reported using the template report (Appendix 10). A CD of the MRI examination will be required. The main aim of the MRI sub-study is the analysis of the initial MRI interpretation and correlation with histopathology report.

In addition CDs of MRIs from a limited group of patients selected by site will be reviewed. Rectal MRI will be performed prior to radiotherapy. Any second MRI performed after radiotherapy will be at the discretion of the treating doctor and will not form a part of the study.

A modified rectal MRI template report prepared by the Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study (MERCURY) will be provided to sites for completion by the reporting radiologist. The template report includes questions about the experience of the reporting radiologist.

MRI staging accuracy

The MRI Staging Accuracy sub-study will address the following questions for analysis:

i) Are there different outcomes based on MRI stage?

ii) What is the staging accuracy of MRI compared to histology in those patients who:
a. did not have preoperative chemo/radiotherapy?
b. did have preoperative chemo/radiotherapy? (i.e. anticipating that chemo/radiotherapy may limit comparison)

iii) Is there a difference in staging accuracy and/or outcomes based on the experience of the reporting radiologist?
iv) Is there a difference in staging accuracy and/or outcomes based on MRI quality?
v) There would be the potential to perform reliability studies on a subset of patients.

Analysis of reports will be lead by a Radiologist, and done in conjunction with statisticians at the NHMRC Clinical Trials Centre.

9.7 Tissue Banking

Patients will be invited at the time of study entry to provide written informed consent for donation of a tissue sample for use in as yet undefined biological / translational sub-studies.

No biological sub-study will be undertaken without approval by a Human Research Ethics Committee (HREC), the AGITG Scientific Assessment Committee, and the Trial Management Committee.

This additional tissue banking consent is not an inclusion criteria for the study and patients may withdraw their consent for tissue banking at any time. Full details are within the template Tissue Banking Patient Informed Consent form (PIC). (Appendix 6)

10. STATISTICAL CONSIDERATIONS

10.1 Trial Size

Based on historical data for standard open resection, we expect the rate of successful resection based on pathological parameters to be 90%. This rate is expected for either the fully open or hybrid procedures. A non-inferiority margin of at most 10% from the successful resection rate with open (laparotomy) for the experimental arm (laparoscopic resection) would still be considered worthwhile based on pathological outcomes. A 10% difference in surgical success rates is expected to be associated with less than a 5% difference in local recurrence rates assuming less than a 2 to 1 association in these outcomes. (The CLASSIC trial demonstrated a 6% higher rate of positive circumferential margins with laparoscopic procedures but this was associated with no observed increase in loco-regional recurrence27).

Analyses will be based on intention-to-treat analyses and hence conversions from laparoscopic to open procedures increase the chance of false positive result. A conversion rate of less than 20% is expected and to account for this a lower non-inferiority margin of 8% has been chosen.

The following table gives the number of patients required to demonstrate non-inferiority based on different non-inferiority margins and 95% confidence (one-tailed) with 90% and 80% power:

<table>
<thead>
<tr>
<th>Margin</th>
<th>90% power</th>
<th>80% power</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0%</td>
<td>430</td>
<td>310</td>
</tr>
<tr>
<td>9.0%</td>
<td>520</td>
<td>380</td>
</tr>
<tr>
<td>8.0%</td>
<td>640</td>
<td>470</td>
</tr>
<tr>
<td>7.0%</td>
<td>810</td>
<td>590</td>
</tr>
</tbody>
</table>

Table 5. Patient numbers required to demonstrate non-inferiority at 90% and 80% power.
Thus a sample size of 470 patients would be sufficient to declare laparoscopic resection non-inferior to open rectal resection with a non-inferiority margin of 8% with 95% confidence and 80% power.

Safety data will be reviewed by the AGITG Independent Data Monitoring Committee (IDMC) on a six-monthly basis. This review will include surgical complications, adverse events and other major outcomes as per the study protocol. Safety data will be reviewed monthly by the Trial Management Committee (TMC) as detailed in Section 10.5.

Additionally an interim analysis on the primary endpoint will be performed after pathological markers for 120 patients in the laparoscopic arm have been obtained from their resected tumours to determine possible futility of the procedure. In this analysis if 31 or more unsuccessful resections are observed in the first 120 patients randomised to the laparoscopic arm (estimated success rate of 74%) consideration will be given to stopping the study.

This boundary is obtained as follows: Suppose after 120 patients in the laparoscopic arm, there are x successes. Now if the study continues to the full sample size (235/arm) and all the remaining cases are successes, the success rate in this group would be \( p_T = \frac{x+115}{235} \). For non-inferiority to be declared we will require that the upper 95% one-sided CI for the difference \( p_C - p_T \) be less than 0.08. Where \( p_C \) is 0.90, the assumed success rate in the control arm, the minimum value of \( p_T \) for which non-inferiority will occur is when \( p_T = 0.87 \) or (205 successes). Therefore if we observed 204 successes we would fail to declare non-inferiority and so if after 120 patients the success rate is 74% or less (89 or fewer successes) then the feasibility of continuing the study will be considered. If feasibility becomes an issue, the success rate in the control group may be used to refine the success rate required in the interim analysis.

The AGITG IDMC will review conversion rates greater than 20% in any individual surgeon.

### 10.2 Statistical Analysis

#### 10.2.1 Primary Analysis

The primary analysis will be according to the intention-to-treat (ITT) principal. Comparisons on the proportion of successful resections in each treatment group will be performed using a test of proportions and the difference between the control and intervention groups together with the 95% CI will be presented. Non-inferiority will be declared if the lower bound of the one-sided 95% CI for the difference between proportions is less than 8%. The notional significance level is 5%. Secondary analyses will adjust for significant prognostic factors using suitable regression models. Results will be provided with estimates and the appropriate confidence intervals where feasible. Time to event outcomes will be described using Kaplan-Meier curves (if appropriate) and proportional hazards models will be used to examine the impact of predictors on these outcomes.

#### QOL and Cost Effectiveness

The QOL analyses will comprise between treatment comparisons using AUC methodology and comparison of the general versus specific measures using the Bland-Altman method. In addition inter-patient changes over time will be examined. Cost-effectiveness analyses will be performed by the Cancer Australia cost-effectiveness group of the Clinical Trial Development Unit (CTDU) at the NHMRC Clinical Trials Centre.

#### 10.2.2 Combined Prospective Meta-analysis

A combined prospective individual patient meta-analysis of A La CaRT and the US Study Z6051 is planned after both studies have completed recruitment (providing a total of 950 patients). This combined analysis will have as its primary outcome loco-regional recurrence after a minimum 3
years follow-up and will provide 90% power to demonstrate non-inferiority of laparoscopic surgery, assuming a non-inferiority margin of 5% difference at 3 years (10% vs. 15%) at a 95% level of significance.

Disease free survival and local pelvic recurrence at 2 years and overall survival at 5 years will also be examined together with relationships between surgical success rates and differences in long-term clinical outcomes. The combined analysis will also examine differences in surgical outcomes by region.

11. STUDY STRUCTURE

The study will be carried out under the auspices of the AGITG. Data collection and management will be performed by the NHMRC Clinical Trials Centre. The Trial Management Committee (TMC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). Statistical analysis will be performed by the NHRMC CTC. The Independent Data Monitoring Committee (IDMC) will provide independent assessment of patient safety and trial progress, making recommendations to the TMC about the continuation of the trial based on data made available by the trial statistician.

12. ADMINISTRATIVE ASPECTS

12.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007) and the principles laid down by the World Medical Association in the 2008. The investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the NHRMC CTC, principal investigator and HREC must be advised immediately.

12.2 Surgeons’ Registration Requirements – Credentialing

The study is limited to participation by pre-approved credentialed surgeons. The study chair or designee will notify each surgeon or group involved in the study when approved. Randomisation by that surgeon may not begin until documentation has been submitted and the study chair has approved his/her laparoscopic experience. (Please refer to Section 8, Quality Assurance and Control - Surgeon Skill Verification).

12.3 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC Clinical Trials Centre, University of Sydney. Information will only be available to authorized representatives of the hospital’s Health Research Ethics Committee, the study sponsor AGITG, staff from the NHMRC Clinical Trials Centre, University of Sydney and regulatory authorities, as required by law, for the purposes of verifying the study procedures or data.

The status of the subject (alive or dead) may be followed up through Australian state-based Cancer Registries annually or as required. Subjects will be asked to give informed consent for access to Cancer Registries.
12.4 Protocol Amendments
Changes and amendments to the protocol can only be made by the Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the Case Report Forms, if required, will be incorporated in the amendment. The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).

12.5 Data Handling and Record Keeping
Trial data will be recorded on the paper or electronic CRFs provided and submitted to the NHRMC CTC. All required data entry fields will be completed. Data corrections will be done according to the instructions provided in the CRF Completion Guidelines and Investigator Site File. The investigator will be asked to confirm the accuracy of completed CRFs by signing paper CRFs as indicated or entering information into the electronic CRF database.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

a. Subject's name, contact information and protocol identification.
b. The date that the subject entered the study, and subject number.
c. A statement that informed consent was obtained (including the date).
d. Relevant medical history
e. Dates of all subject visits and results of key trial parameters.
f. Occurrence and status of any adverse events.
g. The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.

All study-related documentation will be maintained for 15 years following completion of the study.

12.6 Study Monitoring
Data from this study will be monitored by Clinical Trials Program staff from the NHMRC Clinical Trials Centre (CTC). Monitoring will include centralized review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during for source data verification, review of the investigator's site file and drug handling records. The CTC will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the subject gives authorized CTC staff direct access to their medical records and the study data.

12.7 Audit and Inspection
For the purpose of ensuring compliance with Good Clinical Practice and regulatory agency guidelines it may be necessary for the NHMRC CTC / AGITG Co-ordinating Centre or designate or a regulatory agency or HREC to conduct a site audit or an inspection.
By signing the Investigator’s Agreement, the Investigator agrees to allow NHMRC CTC / AGITG Co-ordinating Centre Staff or designate and drug regulatory agencies to have access to their study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

12.8 Publication Policy

Preparation of publications and presentation and the authors of any reports will be decided as per the AGITG publication policy (Appendix 8).
13. REFERENCES


44. Strassburg J, on behalf of the MERCURY study group: Magnetic resonance imaging in rectal cancer: the MERCURY experience. Tech Coloproctol. 2004: S16-S18