# EnROL

Enhanced Recovery Open vs. Laparoscopic
ISRCTN48516968

# Conventional versus laparoscopic surgery for colorectal cancer within an Enhanced Recovery Programme

EnROL Trial Office, Oncology Clinical Trials Office, University of Oxford

Sponsored by the University of Oxford and North West London Hospitals NHS Trust

# EnROL TRIAL CONTACT INFORMATION

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Email: enrol@octo-oxford.org.uk

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## Randomisation Service

24 hours on line randomisation: https://enrol.clinpharm.ox.ac.uk

Queries: Mon-Fri 09:00-17:00 GMT/BST

Tel: 0800 389 1635

Fax: 0800 389 1629 [fax 24 hours*]

*Faxes received outside office hours will be dealt with the next working day

## Clinical Queries

During office hours clinical queries should be directed to the EnROL Trial Office Tel: 01865 617000

The call will be passed on to an EnROL Clinical Coordinator, or an appropriate member of the Trial Management Group.

Out of office hours, call the John Radcliffe Hospital switchboard

Tel: 01865 741166 and ask to call the EnROL Clinical Co-ordinator

## Statistical Centre

EnROL Statistician

Centre for Statistics in Medicine, Wolfson College Annexe, Linton Road, Oxford, OX2 6UD

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# 1 BACKGROUND

## 1.1 EPIDEMIOLOGY

Colorectal cancer is the second commonest malignancy in England and Wales, accounting for approximately 36,000 new cases in 2002 and 17,000 deaths in the same year. Between 35 and 40% of tumours will be rectal cancer, defined as being within 15 cm of the anal verge. About 80% of all patients diagnosed with colorectal cancer (including some with advanced disease) undergo resection: in the vast majority of people, this is performed using conventional 'open' surgery which generally requires a large abdominal incision. Surgery may result in significant comorbidity which is reflected in a postoperative hospital stay of 10-14 days and 30 day mortality of 3-5%. If the morbidity of this surgery can be decreased there is considerable potential to shorten and improve recovery, in addition to releasing hospital beds.

## 1.2 LAPAROSCOPIC SURGERY

Laparoscopic colorectal resection facilitates outcome following surgery due to a reduction in the surgical stress response, decreased operative blood loss, improved pulmonary function and reduced post-operative pain and infection. In a recent meta-analysis[1], hospital stay decreased by 21% as a result of these improvements. In the 4 largest randomised trials reported to date [3-7] reduction in hospital stay was 2.7 days or less, with stays following laparoscopic resection ranging from 5 to 9 days. There is also evidence that laparoscopic surgery is associated with better recovery of quality of life in the early post operative period [8]. Despite this superiority over open surgery laparoscopic resection is not widely used in the UK and results, as measured by hospital stay and reduction in complications, do not compare to those following the use of multimodal rehabilitation, termed an Enhanced Recovery Programme.

## 1.3 ENHANCED RECOVERY PROGRAMMES

Enhanced Recovery Programmes improve recovery to such an extent that hospital stays of 2-3 days have been reported following both laparoscopic and open surgery in Copenhagen [9,10]. Similar results have been reported in two single centre randomised trials, from Britain and America [11,12]. Improvement in outcome is attributed to reduction in the pathophysiological response to stress, improved pain control, reduction in the paralytic ileus, early mobilisation, early feeding and preconditioning of expectations. As a consequence of this, two studies have randomised 60 patients each, attempting to answer the question, does laparoscopic surgery improve outcomes when compared to open surgery, if perioperative care is optimised by using an Enhanced Recovery Programme for both interventions[13,14]. The study from Yeovil[14] demonstrated improved outcomes such as post-operative hospital stay and 30 day re-admission rates whereas that from Copenhagen[13] had identical hospital stays for the laparoscopic and open groups and did not observe significant improvements in recovery after laparoscopic surgery. The Danish study did however, have high re-admission rates in both groups and a trend towards increasing mortality in the open surgery patients.

## 1.4 ONCOLOGICAL OUTCOMES FOLLOWING LAPAROSCOPIC SURGERY

Four studies [3-6] have examined colorectal cancer outcomes by randomising 2288 patients between laparoscopic and open surgery. Early results suggest that both techniques appear to be equally effective at curing cancer. The smallest study[3] suggested there might be an advantage to the laparoscopic approach in stage III cancer but that has not been reproduced in subsequent work. If such an advantage exists its explanation might be the reduced blood transfusion rates following minimal access surgery and/or the decreased immunosuppression that has been observed in experimental work [15,16].

Oncological benefits of the laparoscopic approach may not have been observed in the studies reported to date as high conversion rates to open surgery of 11-23% [3-6] could have masked the beneficial effects of laparoscopic surgery. All of these studies have been undertaken early in the learning curve of laparoscopic colorectal surgery, hence the high conversion rates. During the 4 year period in Yeovil Hospital, starting January 2002, 93% of elective colorectal cancer surgery (excluding 7% of patients who required long course chemoradiotherapy for fixed pelvic tumours) was attempted laparoscopically and only 9% of the group converted to open surgery, showing the benefits of training (personal communication, RH Kennedy).

Laparoscopic colorectal resection is technically 'laparoscopic assisted' as an incision of approximately 4-7 cm is required to remove the specimen. The only truly laparoscopic colorectal resection occurs when an abdominoperineal excision of the rectum is undertaken, the specimen being removed through the perineal wound. When conversion to open surgery is required it is usually defined as the inability to complete the mobilisation of the specimen laparoscopically.

# 2 RATIONALE FOR THE CURRENT STUDY

Laparoscopic resection of colorectal cancer has produced modest improvements in post-operative recovery when compared to conventional surgery, largely resulting from a slight reduction in hospital stay and a decrease in infective complications [1-8]. Greater improvements, as measured by postoperative hospital stay, have resulted from the use of enhanced recovery programmes [9-12]. This study examines the hypothesis that laparoscopic surgery within an enhanced recovery programme will provide superior postoperative outcomes when compared to conventional open resection of colorectal cancer within the same programme.

The National Institute for Health and Clinical Excellence (NICE) recently commissioned an Academic Assessment of laparoscopic surgery in the treatment of colorectal cancer from the Aberdeen Health Technology Assessment Group [17]. Among their recommendations The Assessment suggested further research is required as follows:

- To analyse resources required and costs of both laparoscopic and open surgery.
- To assess wound related morbidity
- To examine outcomes following surgery bearing in mind that laparoscopic resection is technically challenging and that performance is likely to improve with experience.
- To analyse the effectiveness and cost-effectiveness of laparoscopic compared to open surgery when both are optimised within an enhanced recovery programme.

Participating centres will have extensive experience of laparoscopic colorectal resection in order that potential improvements in outcome will not be minimised by high conversion rates. This study will also provide the opportunity to analyse serum and tissue samples in order to examine surrogate markers of oncological outcome when laparoscopic surgery is accompanied by low conversion rates.

The trial has also been designed to allow meta-analysis with data from the COLOR II study. The latter, is an international multicentre trial randomising patients who have rectal cancer to either laparoscopic or open surgery. It is primarily designed to analyse oncological outcomes, and data from the EnROL study will contribute to that, as well as to the secondary outcomes of morbidity, cost and quality of life.

# 3 STUDY OBJECTIVES

Having optimised outcome within an Enhanced Recovery Programme, a randomised trial is required to answer the following questions:

- Does the laparoscopic technique improve patient recovery as measured by physical fatigue, Quality of Life analysis and standardised performance indicators (SPIs), and cosmetic assessment during the 12 months following surgery?
- Does laparoscopic treatment reduce postoperative hospital stay, when compared to open surgery for colorectal cancer?
- Does laparoscopic treatment improve the outcome measures: complications, re-operation and re-admission when compared to open surgery?
- Is laparoscopic surgery an economically viable patient management process as assessed by cost effectiveness and cost utility analysis in the first 6 months after surgery?
- Does laparoscopic surgery affect surrogate markers of oncological outcome? The markers to be defined in a future translational study.

## 3.1 PRIMARY ENDPOINT

Postoperative physical fatigue using the Multidimensional Fatigue Inventory 20 (MFI-20)[18] at 4 weeks after surgery

## 3.2 SECONDARY ENDPOINTS

- Postoperative hospital stay
- 30 day and in-hospital complications
- 30 day re-admission and re-operation rates
- Assessment of health economics using cost effectiveness and cost utility
- Patient reported and functional outcomes (SF-36, SPIs)[19,20]

- Cosmetic assessments
- Translational endpoints (see Section 10 for details)

# 4 STUDY DESIGN

## 4.1 TYPE OF STUDY

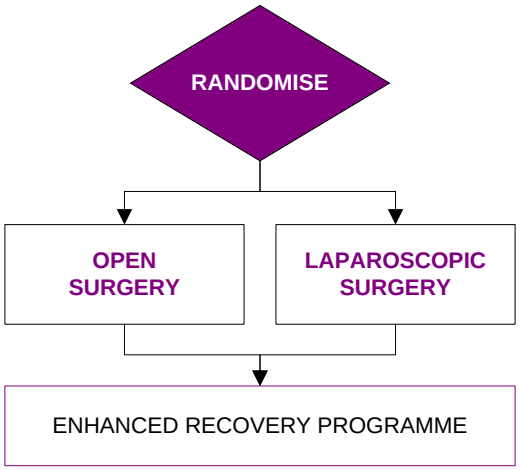
This is a phase III multicentre randomised controlled trial, with blinding of patients and outcome observers during the first week post-operatively.

## 4.2 EXPECTED NUMBER OF SUBJECTS

266 patients recruited from 12 sites, with 133 patients in each arm.

## 4.3 RANDOMISATION PROCEDURES

After completing suitability checks and consent forms (Appendix 5) for a patient, site staff will confirm the eligibility of the patient using a remote electronic data capture (EDC) system and the patient will be randomised to receive one of the interventions below.




# 5 STUDY POPULATION

## 5.1 INCLUSION CRITERIA

1. Diagnosis of colorectal cancer (any stage) (Tumours are defined as being rectal when at or within 15 cm of the anal verge on rigid sigmoidoscopy performed with the patient awake.)
2. Suitable for elective resection following a planned admission
3. ≥18 years of age
4. Written informed consent given

## 5.2 EXCLUSION CRITERIA

1. Acute intestinal obstruction
2. Unplanned admission to hospital
3. Unsuitability for epidural insertion - determined pre-randomisation
4. Pregnant
5. Unsuitable for laparoscopic resection as conversion to open surgery is likely, e.g. fixed tumours or rectosigmoid cancers which have a ‘threatened margin’ (defined as tumour at or within 1mm of the circumferential resection margin) on preoperative imaging.
6. Previous complex laparotomies

# 6 THE ENHANCED RECOVERY PROGRAMME AND PATIENT CARE

## 6.1 PREOPERATIVE INVESTIGATIONS

Prior to surgery, all patients should undergo complete colonic imaging by colonoscopy, barium enema or CT scanning. Preoperative imaging should also include the chest and liver - preferably using CT. For rectal cancer, MRI of the rectum should be undertaken to exclude a 'threatened margin'.

## 6.2 PREOPERATIVE RADIOTHERAPY AND CHEMOTHERAPY

Pre-operative radiotherapy may be used in rectal cancer but should be standardised at each site irrespective of the randomisation and treatment details recorded for each patient. Long course preoperative chemoradiotherapy is not a trial exclusion criterion except when used to treat a 'threatened margin' in rectal cancer.

## 6.3 PROTOCOL FOR PATIENT MANAGEMENT

**INCLUDING KEY FEATURES OF THE ENHANCED RECOVERY PROTOCOL (ERP) AND CRITERIA FOR DISCHARGE**

| | |
|---|---|
| **Before admission** | • Conditioning of expectations of patient and carer by receipt of oral and written information at a dedicated preadmission visit, or by telephone counselling, with provision of a dedicated booklet or video sent by post.<br>• Meeting with stoma nurse if stoma anticipated.<br>• Identification of factors that might delay discharge and consideration of solutions e.g. provision of support when discharged if living alone.<br>• Co-morbid risk assessment: optimised pre-morbid health status. |
| **Day before surgery** | • Avoidance of oral bowel preparation except in patients undergoing total mesorectal excision (TME) and reconstruction.<br>• Nutrition: three high protein/high calorie drinks if receiving oral bowel preparation. |
| **Day of surgery** | |
| **Pre-operatively** | • Preoperative oral carbohydrate loading to be given 2-4 hours prior to anaesthesia, using ≥ 200mls of fluid containing ≥ 12.5g/100mls CHO with a proven safety profile.<br>• Avoidance of long acting sedative medication from midnight prior to surgery. |
| **In theatre** | • Activation of thoracic epidural (T6-11) prior to skin incision.<br>• Avoidance of abdominal drains at primary operation.<br>• Avoidance of nasogastric drainage in the immediate postoperative period.<br>• Total volume of IV fluid < 3000ml.<br>• The use of upper body forced air heating intraoperatively.<br>• Local anaesthetic infiltration to the largest wound in minimal access surgery.<br>• Open surgery: small transverse or curved incisions when possible. |
| **After theatre** | • Oral intake of ≥ 800ml fluid (including oral nutritional supplements) postoperatively on the day of surgery, before midnight.<br>• ≥ 200ml oral nutritional supplement postoperatively on the day of surgery, before midnight.<br>• Mobilisation by walking or sitting in a chair. |
| **First Postoperative day from midnight – midnight (Day 1)** | • ≥ 2 units of oral nutritional supplement taken.<br>• Termination of IV fluid infusion.<br>• Intake and tolerance of solid food.<br>• Intake of lactulose or a magnesium preparation to enhance bowel movements.<br>• Use of thoracic epidural analgesia.<br>• Mobilisation (out of bed) for at least 6 hours.<br>• Assisted mobilisation – 4 x 60m walks. |
| **Second Postoperative day from midnight – midnight (Day 2)** | • Pain relief: termination of the thoracic epidural analgesia.<br>• Use of a multi-modal analgesic regime at, or before, discontinuation of thoracic epidural analgesia e.g. paracetamol and non steroidal anti-inflammatory or equivalent.<br>• Termination of urinary drainage on day 2 or earlier, except after TME when it may be preferable to leave it until day 3. |

| | |
|---|---|
| **Discharge** | • Aim for discharge day 2-3 for colons and proximal rectums; day 5 when a stoma fashioned.<br>• Discharge Criteria: patients must be tolerating normal food, mobilising independently and be managed on oral analgesics to fulfil discharge criteria.<br>• Follow up: provision of hospital contact numbers to allow discussion of problems; expedited review on ward if problems within 2 weeks of surgery.<br>• Review in out patient clinic at two weeks post operation. |

It is possible for individual centres to amend this programme provided the treatment is standardised irrespective of randomisation and that the Trial Office is notified prior to the centre opening to recruitment. Compliance with the components of the Enhanced Recovery Programme will be assessed via the ERP Compliance eCRF on a per patient basis.

### 6.4 ANAESTHETIC CARE

This should be standardised in each centre irrespective of the randomisation. Guidelines for anaesthetic care are given in Appendix 10.

### 6.5 SURGICAL PROCEDURE

Surgery should be carried out in a standard fashion by the trial surgeon(s) at each site, the only difference being the method of access. Further details are given in Appendix 9. Rectal tumours within 10 cm of the anal verge should be treated by total mesorectal excision accompanied, whenever possible, by preservation of the hypogastric nerves. Tumours are defined as being rectal when at or within 15 cm of the anal verge on rigid sigmoidoscopy performed with the patient awake.

### 6.6 QUALITY CONTROL OF SURGERY

To enter the trial each surgeon must have performed more than 100 laparoscopic colorectal resections and more than 50 open total mesorectal excisions for rectal cancer. All surgeons will be provided with video recordings of standardised laparoscopic operative procedures which have been prepared for the Laparoscopic Colorectal Preceptorship Programme. Macroscopic assessment of the quality of mesorectal dissection (see section 0) will be provided to each surgeon.

### 6.7 POSTOPERATIVE CHEMOTHERAPY OR RADIOTHERAPY

Postoperative chemotherapy or radiotherapy may be used but should be standardised at each site irrespective of randomisation and treatment details recorded for each patient.

### 6.8 OUTPATIENT FOLLOW UP AND INVESTIGATIONS

Patients should be seen at 2 weeks, 4 weeks, 3 months, and 6 months following surgery.

## 7 MEASUREMENT OF OUTCOME

The analysis of this trial is on an intention to treat basis. This means that all patients will be analysed based on the treatment allocated at randomisation, not that actually received. It is therefore important that every effort is made to encourage all patients to attend for follow-up clinic visits and complete the questionnaires to avoid bias in the analysis of the results.

### 7.1 FATIGUE

Fatigue will be assessed using the Multidimensional Fatigue Inventory 20 (MFI-20) [18].

### 7.2 POSTOPERATIVE HOSPITAL STAY

Counting the day of operation as day zero.

### 7.3 COMPLICATIONS, RE-ADMISSION AND RE-OPERATION RATES

30 day morbidity will be assessed by the site's Research Nurse using a standardised definition of complications (Appendix 2) at 4 weeks post-operatively. 30 day re-admission and re-operation rates, along

with 30 day and in-hospital mortality will also be recorded.

### 7.4 PATIENT REPORTED AND FUNCTIONAL OUTCOMES

Self-reported quality of life will be assessed using the Short Form 36 questionnaire (SF-36) [19].

Functional outcomes will be measured using standardised objective performance indicators (SPIs) using a standard test of lower limb strength, balance and endurance that takes approximately 5 minutes to measure[20].

### 7.5 COSMETIC OUTCOMES

Cosmetic outcome, to assess the impact of surgery on the appearance of the body and the patient's confidence, will be assessed using a Body Image Scale Questionnaire [22].

### 7.6 HEALTH ECONOMICS OUTCOMES

Health Economics questionnaires will be completed by all patients providing information about the use of healthcare post-operatively for 6 months. Data collected will include GP surgery visits, GP home visits, in-patient stays, out-patients visits, District Nurse visits and Physiotherapy and stoma nurse usage. In addition, EuroQol (EQ-5D) questionnaires will be completed.

Data will also be collected from the medical records to calculate the relative cost of the operative and peri-operative period (costs to be calculated include in-patient hotel costs, in-patient, treatments costs [including re-admission and re-operation within 30 days and convalescent care], operating theatre costs and drug costs).

## 8 DATA COLLECTION

The EnROL trial Data Management System is based entirely on electronic submissions of data via Web page: https://enrol.clinpharm.ox.ac.uk.

The system has been designed for ease-of-use data entry and monitoring the quality of incoming records.

To access the EnROL Website all authorised users need to complete the Password Request section of the Staff Contact & Responsibilities Sheet. A unique password will be issued for each user responsible for data entry. A Staff Contact & Responsibilities Sheet is available from the EnROL Trial Office.

A guide explaining how to use the EnROL Website will be provided to every site and is available on request from the EnROL Trial Office.

### 8.1 CRF COMPLETION

The data requirements for EnROL and time points for submission are included in Appendix 3 of this protocol.

The Principal Investigator has an overall responsibility for the timing, completeness and accuracy of the electronic Case Report Forms (eCRFs). Data collected on each subject will be entered by the Principal Investigator, or his designee (as noted on the Staff Contact & Responsibilities Sheet), as accurately and completely as possible. The Principal Investigator will allow study staff access to any required background data from such records (source data e.g. medical records) on request.

For occasions when it is not possible to enter data directly on the EnROL Website, worksheets, which will be provided for each eCRF, should be completed. Each worksheet must be transcribed into electronic CRFs by an authorised person, as stated on the Staff Contact & Responsibilities Sheet, as soon as possible and the worksheets retained for future reference and monitoring purposes.

**Please ensure that all data submitted are verifiable in the source documentation or the discrepancies explained adequately**.

### 8.2 QUESTIONNAIRE COMPLETION & FUNCTIONAL OUTCOME DATA

The MFI-20, SF-36, EQ-5D and Health Economics Questionnaires and Body Image Scale Questionnaire are to be completed by the patient with support from the site's Research Nurse, within 4 weeks prior to surgery.

MFI-20, SF-36, EQ-5D and the Health Economics Questionnaires are then to be completed by the patient at 4 weeks, 3 and 6 months postoperatively. The Body Image Scale is to be completed by the patient at 6 and

12 months postoperatively. The questionnaires should be given to patients at an outpatient clinic (if the patient has left hospital) or be sent by post.

Once completed, questionnaires must be posted to the EnROL Trial Office:

FREEPOST RRTL-ALZY-CBRL
EnROL Trial Office
Oncology Clinical Trials Office (OCTO)
Department of Clinical Pharmacology
University of Oxford
Old Road Campus Research Building
Old Road Campus, off Roosevelt Drive
Headington
Oxford, OX3 7DQ

If the questionnaires are not/cannot be completed, the reason for non-completion should be recorded on a Non-Completion of Questionnaires record and the record posted to the EnROL Trial Office.

SPIs are to be measured within 4 weeks prior to surgery and then at 4 weeks, 3 and 6 months post-operatively and reported on the appropriate eCRFs.

### 8.3 BLINDING SUCCESS

Blinding is an important design feature of randomised controlled trials, reducing the risk of several forms of bias including reporting bias and observer bias. A successfully implemented blinding protocol improves the validity of trial results, however the success of blinding is infrequently tested or reported in randomised controlled trials. To investigate the role and success of blinding in surgical randomised controlled trials, and its impact on patient experience, quantitative data about the success of blinding will be collected using the Bang Blinding Index[30]. This statistical measure calculates the proportion of un-blinded patients (and research staff) in a trial by asking them to state which arm of the study they believe they/their patient have been allocated to. The results will be combined and compared with data collected from another surgical trial (EWIC) to gain a broad-based understanding of the role and impact of blinding in surgical trials.

The Patient Operation Experience questionnaire and Staff Blinding Experience questionnaire are to be completed by the Patient and site Research Nurse (or equivalent) respectively on day 1 post surgery and again prior to unblinding on either the day of discharge (if earlier than day 7) or day 7 post surgery. The data captured will be reported to the EnROL Trial Office on the 30 Day Post Surgery eCRF.

### 8.4 DATA TO BE COLLECTED BY THE PATHOLOGIST

Detailed pathological examination of resected specimens will be undertaken by a nominated local pathologist, according to the RCPath guidelines with minor additions (Quirke & Williams 1998) [23]. Staging will be version 5 of TNM. Training is available if needed. For more information, contact the EnROL Trial Office.

Pathologists will receive the surgical specimen either in formalin or fresh. Details of the method can be found in Appendix 1 and are available on the Pathology Data CD which accompanies the Protocol. If the CD is not available, please contact the EnROL Trial Office for a replacement copy.

Central review of the histology will be performed to audit the surgeon/pathology; either the original diagnostic sections, which will be copied and then returned to the relevant participating hospital, or a second set of haematoxylin and eosin sections should be sent to the EnROL Trial Office along with three colour digital files of the specimen and cut slices. Two extra blocks of tumour and one block of normal should also be taken and sent to the Trial Office. The proforma for reporting is provided in the Investigator File and copies are also available from the EnROL Trial Office. Following completion by the Pathologist, the form must be transcribed by an authorised person at the site into the EnROL website.

## 9 STATISTICS

### 9.1 RANDOMISATION AND TREATMENT ALLOCATION

Following consent, a patient is entered into the trial using a remote EDC system. Sites will access the system locally via the internet, using a username and password.

Randomisation will be by minimisation, using the following factors

- hospital in order to avoid bias

- site of cancer, i.e. – between rectum and colon, as hospital stay, stoma rates and complications differ between the two groups. **Please note tumours are defined as being rectal when at or within 15 cm of the anal verge on rigid sigmoidoscopy performed with the patient awake.**
- age: <66, 66-75, >75

The first 50 patients will be assigned treatment by simple randomisation and the remaining patients will be assigned with a probability of 0.8 the treatment that most reduces the imbalance of the above factors.

## 9.2 ANALYSIS PLAN IN SUMMARY

All analyses will be on an intention-to-treat basis. This means that patients will be analysed as they are randomised irrespective of the treatment actually received.

The primary outcome will be fatigue as measured by the MFI-20 at four weeks post surgery. If the primary outcome is normally distributed it will be compared using a t-test, ANCOVA adjusting for the minimisation factors (primary analysis) and ANCOVA with further adjustment for prognostic factors.

Fatigue will also be compared at three and six months, the remaining quality of life variables at 4 weeks, 3 and 6 months, and the cosmetic outcome at 6 and 12 months, using the same analyses as for the primary outcome.

For all continuous outcome variables, if there is severe departure from Normality the first approach will be transformation. If the data cannot be transformed to Normality, a Mann-Whitney test will be used. In the latter case no adjustment will be made for the minimisation or prognostic factors. Hospital stay will be compared using Kaplan Meier plots and log rank tests. The complications, re-operation and re-admissions data will be binary and will hence be compared between the randomisation groups using a chi square test (or Fisher exact test if the data is sparse).

## 9.3 SAMPLE SIZE

Using fatigue as the primary outcome (MFI-20: multidimensional fatigue inventory 20) sample size has been estimated as in the recent study by Kok et al[29]. There is a 90% power to detect a difference of 0.45 standard deviations at p=0.05 (two-tailed) with 133 patients in each group (including allowance of 15% for loss to follow up and a conversion rate of 8% – see 2.10.15).

Some other variations are shown in the following table

| Δ | Sample size per group | Total trial size, including allowance for 15% loss to follow up | Total trial size, including allowance for 15% loss to follow up and 8% conversion |
|---|---|---|---|
| 0.4 | 131 | 308 | 332 |
| 0.45 | 104 | 246 | 266 |
| 0.5 | 82 | 194 | 210 |
| 0.6 | 58 | 136 | 148 |

The study is also powered to detect a difference in postoperative hospital stay: we expect 60% of patients to have colonic cancer resulting in an estimated 3 day hospital stay after laparoscopy and 6 day hospital stay after open surgery. 40% of patients are expected to have rectal cancer with an estimated 6 day hospital stay after laparoscopy and 9 day hospital stay after open surgery. Therefore overall for laparoscopic patients we would expect a 4 day stay and for open patients a 7 day stay. With an estimated standard deviation of 7, the planned sample size of 133 per group will give 90% power to detect a difference at p=0.05 (two-tailed) (266 patients in total) with a 15% allowance for loss to follow-up.

## 9.4 ANALYSIS OF HEALTH ECONOMICS DATA

A health economist will carry out the analysis of the health economics data to determine if laparoscopic surgery is an economically viable patient management process as assessed by cost effectiveness and cost utility analysis in the first 6 months after surgery.

Costs will be estimated from the perspective of the UK NHS and health benefits expressed in terms of quality-adjusted life-years (QALYs). The cases where laparoscopic surgery may be considered cost effective will be pre-defined and the mean differential costs and QALYs will be calculated in order to assess whether any of these conditions are satisfied.

The relative costs of the operative and peri-operative period will be derived for all trial patients including the

cost of consumables that are likely to differ between the two surgical procedures.

QALYs will be calculated for each patient in the trial, on the basis of their responses to the EQ-5D pre-operatively, at one month, three months and six months. Given that the time horizon of the analysis will be less than one year, total costs and QALYs remain undiscounted. To account for the skewed nature of the data, 95% CIs for the differential costs and QALYs will be calculated using non-parametric bootstrapping. In some patients, resource use data and EQ-5D responses may be wholly or partially missing. Missing data will be imputed using a multivariate multiple imputation procedure (Solas 3.0).

Statistical analysis will be undertaken using Stata 10.0.

## 10 TRANSLATIONAL RESEARCH

There is a theoretical oncological advantage to laparoscopic cancer surgery secondary to reduced immunosuppression per se [13] and also decreased blood loss, as blood transfusion worsens outcome [14]. One randomised trial has reported an increased cancer related survival in stage III cancer [3] following laparoscopic surgery, but this was not confirmed in subsequent studies [4-6]. The EnROL trial would provide the opportunity to analyse immunosuppression in a large number of randomised patients and determine its potential effect on oncological outcome. Previous work has demonstrated that the presence of a systemic inflammatory response predicts a poor outcome [24].The measurement of multiple pro- and anti-inflammatory cytokines, cytokine receptors and protein measurements in plasma and serum is proposed and funding is to be sought.

Metabonomics is a rapidly evolving field of biomedical science and is defined as the quantitative measurement of time-related multiparametric metabolic responses of multicellular systems to pathophysiological stimuli or genetic modification. In practice, this involves the use of spectroscopic metabolic profiling methods applied to various body compartments including urine, plasma, stool and tissue, coupled with multivariate statistical analysis of the data, and provides a systems approach for studying *in vivo* metabolic profiles and may aid in identification of novel biomarkers to predict surgical and/or oncological outcomes.

**Measurement of cytokines and VEGF response following surgery**

12 ml of blood (2 x 6ml tubes) will be taken for storage immediately preoperatively, immediately postoperatively and at 24, 48 and 72 hours after surgery. Further samples will be taken at 2 and 4 weeks follow-up. Peripheral blood samples will be collected in heparin coated tubes and returned using the packaging provided.

Samples will be analysed for IL-1beta, IL-6, IL-8, IL-10, TNF-alpha, VEGF and IGFBP-3 using enzyme-linked immunosorbent assay (ELISA).

**Detection of circulating tumour cells after surgery**

5 ml of blood (2 PAXgene™ tubes) will be taken immediately preoperatively and at 24 and 72 hours and then at 2 weeks after surgery and returned using the packaging provided. These samples should be taken after the above blood samples to avoid epithelial cell contamination.

The presence of colorectal cells will be determined by using reverse-transcriptase polymerase chain reaction (RT-PCR) to detect for CEA and Cytokeratin 20 mRNA.

**Metabonomics**

10ml urine samples will be collected at the same time points as blood samples collected for cytokine and VEGF response analyses.

For all samples (blood & urine) deviation times should be as consistent as possible (ideally within 6 hours) with respect to the time of day as circadian rhythm affects metabolic rate and cytokine profile will change. All samples should be posted as soon as possible after collection and should not be stored at the site for sending with later samples.

All samples will be stored at -80˚C upon receipt.

Samples should not be taken from patients who are known to be HIV, HBV or HCV positive. Samples which may contain any other infectious material should not be submitted.

## 11 STUDY ORGANISATION

This is a phase III, multicentre trial co-sponsored by the University of Oxford and the North West London Hospitals NHS Trust.

The study is being conducted on behalf of the NCRI Colorectal Clinical Study Group with independent peer review from CTAAC. EnROL is an independent, investigator led trial run with a study grant from The Bobby Moore Fund, Cancer Research UK, (Study number: CRUK/07/019).

EnROL is an NCRN study (National Cancer Research Network, England, www.ncrn.org.uk).

A maximum of 12 sites will be involved in order to enrol 266 patients with all patients being followed up for a maximum of 1 year after surgery Recruitment will cease in early 2012 unless the recruitment target has been reached prior to this date.

### 11.1 STUDY SITE RESPONSIBILITIES

The Principal Investigator (the lead clinician for the study site) has overall responsibility for the study and all patients entered into the study, but may delegate responsibility to other members of the site team as appropriate e.g. data entry into the EDC system by the Research Nurse. The Principal Investigator must ensure that all staff involved in the study are adequately trained and their duties have been logged on the Staff Contact & Responsibilities Sheet.

For further information on trial responsibilities, please refer to the ICH GCP guideline (E6). Copies can be obtained from the EnROL Trial Office or printed from www.ich.org.

### 11.2 TRIAL COMMITTEES

**Trial Management Group**

The Trial Management Group (TMG) will consist of those running the trial on a day-to-day basis, including the Chief Investigator, staff from the EnROL Trial Office and collaborators. The TMG will meet regularly (at least every 6 months), face to face or by telephone conference call, to discuss trial progress and any issues arising.

**Trial Steering Committee**

The Trial Steering Committee (TSC) for this trial will consist of four independent members. This Committee will meet every nine months, timed to be approximately 1 month after the DSMC meeting. The TSC will assess trial progress and provide recommendations to the TMG.

**Data and Safety Monitoring Committee**

An independent Data and Safety Monitoring Committee (DSMC) will be established for this trial, consisting of 1 clinician, 1 pathologist and 1 statistician, to safeguard the interests of trial participants, potential participants and future patients. It is intended that this committee will meet before accrual commences (or soon after) and then every 9 months (or 90 patients, whichever is the longer), the exact frequency will depend on the rate of accrual and event rates, and may be increased upon request by the Committee. The DSMC will monitor the overall conduct of the clinical trial including recruitment to the trial, protocol compliance, as well as safety and efficacy, taking into account relevant worldwide experience.

The DSMC members and the Chief Investigator work to an agreed charter, with the DSMC making recommendations to the TSC and TMG, providing reports for the main Research Ethics Committee reviewing the trial and for the trial funder.

### 11.3 END OF THE TRIAL

All patients will be followed up for 12 months after surgery or until the end of June 2012, whichever is first. The trial will therefore end on the 30th June 2012. Data cleaning and analysis will then continue up to the 30th September 2012.

## 12 STUDY PROCEDURES

### 12.1 STUDY START-UP

Sites wanting to take part in the study should contact the EnROL Trial Office to obtain trial information and start-up packs (containing relevant core documents and ethics submission information/documents). A Principal Investigator must lead the study at each site, providing the EnROL Trial Office with all core documentation and attend an Investigator Meeting or participate in an investigator call before the site becomes activated. The Trial Office will call to check that the site has all the required study information/documentation and is ready to recruit. The site will then be notified by fax or email once they are activated on the EnROL database and able to randomise.

### 12.1.1 CORE DOCUMENTS

These documents consist of:

- Clinical Trial Agreement
- Staff Contact & Responsibilities Sheet
- Trust R&D approval letter
- All Investigators and Co-Investigators will provide an up to date copy of their CV, personally signed and dated, prior to participating in the study. The CV should detail the Investigators' education, training including training in Good Clinical Practice (GCP) and experience relevant to their role in this study. All investigators will be contacted every three years and asked to submit a current CV.

If circumstances change at the site (e.g. change of Principal Investigator, hospital address etc) then new documents should be completed and sent with a cover letter to the EnROL Trial Office.

## 12.2 RANDOMISATION OF PATIENTS

The Investigator, or his designee (as noted on the Staff Contact & Responsibilities Sheet), must complete and submit electronically a Randomisation Form via webpage https://.enrol.clinpharm.ox.ac.uk prior to randomisation and confirm the patient's randomisation details by eSignature.

The next trial number for the site will be issued and the patient randomly assigned to a treatment arm. The treatment assigned will be hidden from the research nurse and patient until 7 days after surgery.

An email confirming the randomisation and treatment assigned will be sent to the surgeon and to the EnROL Trial Office. A sealed, tamper evident envelope confirming randomisation details will also be sent to the patient's surgeon.

Randomisation via the website is available 24 hours.

In the unlikely event of problems with electronic submission, the EnROL team at OCTO should be contacted:

Mon-Fri, 09:00-17:00 UK time, fax available 24 hours (will be dealt with during office hours, faxes received after 17:00 will be processed the next working day).

Tel: 0800 389 1635 Fax: 0800 389 1629

After patients have been randomised, the Investigator must send a letter to the patient's G.P. (see Appendix 8). Patients should be given a patient card (provided in the Investigator File) detailing the study, emergency contact details. They should be instructed to carry it at all times.

## 12.3 TIMING OF RANDOMISATION

Patients must undergo surgery within 6 weeks of randomisation.

## 12.4 BLINDING OF PATIENTS AND OUTCOME OBSERVERS

Patients and outcome observers will be blinded to the type of surgery (open or laparoscopic) until 7 days after surgery (counting the day of surgery as day 0) or until discharge, if earlier.

Large ALLEVYN adhesive dressings will be provided to participating sites by the EnROL Trial Office for the dressing of patient's surgical wounds. Dressings should be positioned similarly on all trial patients regardless of the type of surgery. The first dressing should be applied by the surgical team and then changed every two days by a nurse not routinely involved with the patient's care. Sites should ensure that patients are not unblinded during the changing of dressings. Dressings will be supplied as part of the set up process, with additional dressings being supplied as required. Sites concerned about the stock level of dressing should contact the EnROL Trial

To assist with the blinding, sites will be provided with labelled envelopes in which the surgical and any other relevant notes can be stored during the blinded period. The front and back of the envelope should be completed with the relevant details, then the sealed envelopes added to the patient's hospital notes to ensure the information is available if needed. Upon opening the relevant details should be added to the envelope and the opened envelope retained as evidence of appropriate blinding of the patient.

The unblinding of a patient is at the discretion of the site, however should any patient be prematurely unblinded this should be recorded in the notes and reported to OCTO on the relevant eCRF.

### 12.5 STUDY DOCUMENTATION

The EnROL Trial Office will provide an Investigator File to each investigational site, including: contact details, patient cards, CRF worksheets, study procedures and all other documents required for completion of the study. Further copies of documents are available from the EnROL Trial Office upon request.

The EnROL Trial Office must review and approve any changes made to any study documentation including Patient Information and Consent Forms prior to use on site.

A Screening Log must be kept of all patients considered for the study and subsequently excluded; the reason for exclusion must be recorded on this form. This allows the EnROL team to assess how well screening is going at each site, to check if the eligibility criteria are appropriate and to identify barriers to recruitment. Screening Logs must be sent to the EnROL Trial Office monthly or as requested.

Upon discharge patients must be provided with a copy of the Discharge Information Leaflet (Appendix 8) or equivalent local information. Patients must be advised that they should contact the hospital in the first instance, not their GP, should they have any concerns or problems in the first two weeks after surgery.

### 12.6 WITHDRAWAL OF PATIENTS

A patient can decide to withdraw from the study at any time. The Investigator also has the right to withdraw patients from the study if he/she feels that it is in the best interests of the patient. Patients should continue to be followed up unless the patient withdraws their consent to any further participation in the study (treatment and follow-up). In this situation a Consent Withdrawal Form (Appendix 7) should be completed and retained at the study site. A Consent Withdrawal Notification eCRF should also be completed and submitted to the EnROL Trial Office via the EnROL Website.

## 13 ETHICAL AND REGULATORY STANDARDS

### 13.1 ETHICAL PRINCIPLES

The trial will be coordinated by the EnROL Trial Office at The University of Oxford in the UK. The office will conduct the trial according to its local adoption of the EU Directive on Clinical Trials and OCTO SOPs. Copies of the EU Directive can be obtained from the EnROL Trial Office upon request.

Patients have the right to withdraw from the study at any time for any reason.

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and subsequent amendments. Copies can be obtained from the EnROL Trial Office or via the internet: http://www.wma.net

### 13.2 INFORMED CONSENT

It is the responsibility of the Principal Investigator (or designee as listed on the Staff Contact & Responsibilities Sheet and locally approved) to obtain written informed consent in compliance with national requirements from each patient prior to entering the trial or, where relevant, prior to evaluating the patient's suitability for the study. The trial should be discussed by one of the research team listed on the Staff Contact & Responsibilities Sheet (clinician or nurse) with the patient in detail and the patient provided with a copy of the information sheet (Appendix 4) to take away with them to consider further. Patients should be given sufficient time to consider the study, allowing time for discussion with family/friends and their GP, and for the patient to ask questions of the research team prior to written consent being given. It is recommended that patients are given at least one day to consider the study before giving consent. However, this is at the discretion of the Principal Investigator. Copies of the Patient Information Sheet and signed Consent Form must be given to the patient. The original Consent Form, signed and dated by the patient and investigator (or designee) must be retained on site. It is recommended that the original is stored in the Investigator Site File with a copy added to the patient's hospital records. Copies of completed Consent Forms must not be sent to the EnROL Trial Office.

### 13.3 ETHICAL REVIEW

The EnROL Trial Office will put the study protocol and any amendments through a main Research Ethics Committee (main REC) in the UK.

The Principal Investigator at each site must submit this protocol, any supporting documentation and any amendments, to a Local Research Ethics Committee or similar body (LREC/R&D) as per local SOPs and in line with favourable opinions and recommendations given by the Main REC. A Site Specific Assessment

(SSA) using the Site Specific Information Form will be required to undertake the trial.

### 13.4 ANNUAL REPORT

The EnROL Trial Office will send an annual trial update report to the main Research Ethics Committee, which will be distributed to all study sites. If required by the local committees (LREC & R&D), it is the responsibility of each study site to send a copy of this report onto their local committees with any extra local information. Additional data required by local committees are available from the EnROL Trial Office on request.

### 13.5 INDEMNITY

This study has been developed by Mr Robin Kennedy and endorsed by the surgical subcommittee of the NCRI Colorectal Clinical Study Group. Peer review was undertaken by CTAAC and funded by an educational grant from Cancer Research UK.

Trial indemnity is provided by the University of Oxford, by their insurance policy, covering non-negligent harm for procedures related to the protocol.

### 13.6 PATIENT CONFIDENTIALITY

The personal data recorded on all documents will be regarded as confidential, and to preserve each patient's anonymity, only their initials and date of birth will be recorded on the CRFs. The Principal Investigator must ensure the patient's anonymity is maintained.

For all patients who consent to information held by the NHS and records maintained by The NHS Information Centre being used to keep in touch with them and follow up their health status, the patient's name and NHS number will be collected once, at randomisation, to allow flagging with the Medical Research Information Centre (MRIS) at The NHS Information Centre. It is envisaged that MRIS would be used to provide current status checks on randomised patients that are lost to follow-up.

The EnROL Trial Office will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which subjects could be identified other than to provide the necessary information required to flag patients with MRIS (see above). Patients should be reassured that their confidentiality will be respected at all times.

The Principal Investigator must keep a separate log of patients' trial numbers, names, addresses and hospital numbers to enable patients to be tracked. The Principal Investigator must maintain documents not for submission to the EnROL Trial Office, e.g. patients' written Consent Forms, in strict confidence in a secure area.

EnROL staff will need access to patient medical notes/records (source data) on-site during routine monitoring visits. An independent internal audit team and inspectors from a regulatory body(s) may visit the site and will require access to source data. In the case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

## 14 QUALITY ASSURANCE

### 14.1 PROTOCOL COMPLIANCE

All study sites taking part in the trial will be required to attend a start-up meeting to ensure compliance with the protocol and allow training on study procedures and data collection methods. This will be a face-to-face meeting including all sites participating, but staff not able to attend or staff joining the team at a later date will be trained on the protocol by telephone conference call, arranged by the EnROL Trial Office.

The EnROL Trial Office will monitor the compliance of study sites taking part in the trial on an ongoing basis. Where non-compliance with the protocol or the standard procedures set out in the Investigator Agreement is suspected, the Chief Investigator for the study will contact the study site to resolve any problems. If appropriate, the matter will be referred to the EnROL Trial Management Group at their next meeting or by correspondence with members if urgent.

The EnROL Trial Management Group has the full authority to take appropriate corrective action, including temporary or permanent withdrawal of the study site from EnROL and other studies run by the trials group.

## 14.2 MONITORING AND AUDIT

### 14.2.1 CENTRAL MONITORING

Study sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. All changes to data that could influence the outcome will be queried with and approved by the study site in a timely manner. For all other data, where there is no doubt about the source of any errors, clear changes to data will be made internally by OCTO staff without referring back to the study site. Study staff will be in regular contact with site personnel (by phone/fax/email/letter) to check on progress and deal with any queries that they may have including those arising from queries raised by the trials office.

### 14.2.2 ON-SITE MONITORING

All participating study sites will be visited by a member of the OCTO monitoring team. The Principal Investigator will allow the study staff access to source documents as requested. Investigators and site staff will be notified in advance about forthcoming monitoring visits.

### 14.2.3 AUDIT

A random sample of approximately 10% of patients entered into EnROL will be audited by an independent internal audit team. The Principal Investigator will allow the study staff access to source documents as requested. Sites will be notified of an audit in advance.

# 15 STUDY ADMINISTRATION

The University of Oxford is registered under the Data Protection Act (1998) for the purpose of research and statistical analysis (health), registration number Z575783X (for more details contact the EnROL Trial Office).

## 15.1 COMPUTERISED RECORDS

**Create data** - Details of study sites and participating staff will be recorded during the study. Patient data records will be created at randomisation and data entered from CRFs during follow up.

**Modify and maintain data** - Records of study sites and participating staff will be modified to maintain accurate details of personnel and status. Data from CRFs will be modified to correct any erroneous or missing entries. The reason for these changes will be recorded in an audit trail.

**Archive** - At the conclusion of the trial, when all patient data has been collected, and the analysis is complete, all of the data stored on the computer system will be archived. After trial conclusion, if any audit is required or new analysis to be performed, the data will be retrieved.

## 15.2 PUBLICATION AND INTELLECTUAL PROPERTY

The EnROL Trial Management Group (TMG) is responsible for approving the content and distribution of all publications, abstracts and presentations arising from the study and for assuring the confidentiality and integrity of the study. It will provide collaborators with approved publicity material and information updates at regular intervals during the course of the study. The definitive publications from EnROL will be written with input from the collaborative group(s) and will acknowledge all those who have contributed to the study.

For these reasons, individuals wishing to present or publish material arising from EnROL should not do so without the written approval of the TMG. All authors must agree to submit a copy of any manuscript and/or abstract for review and comment by the TMG at least sixty (60) days prior to its submission for publication. The TMG will respond with any requested revisions and authors must agree to delete any confidential information and make any corrections of fact before submitting the document for publication. If requested the TMG will take reasonable steps to expedite the review process to meet the author's publication deadlines. Such approval will not be forthcoming until the unblinded, multicentre trial results have been published.

The data arising from EnROL will belong to the University of Oxford and the TMG shall act as custodian of this data.

## 15.3 ARCHIVING

At the end of the trial each site will be provided with a copy of the data submitted as eCRFs for their patients.

All source and study documentation must be securely retained by the Investigator for at least 15 years after the end of the trial. The EnROL Trial Office staff will advise sites of storage requirements upon the study being closed.

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# APPENDIX 1: PATHOLOGISTS' BRIEFING

## Method for dissection of rectal carcinoma resections

The resected specimen is received, fresh or fixed, opened anteriorly except for the area of the tumour and pinned under gentle tension to a cork board for fixation in formalin or floated free in a vat. Once fixed, the anterior and posterior aspect of the specimen should be photographed with a cm scale, and then two 2cm x 2cm colour digital photographs should be produced, one of the anterior surface and one of the posterior surface.

After fixation, the peritoneal reflection is identified and the relative position of the tumour recorded, i.e. below peritoneum (below), partially covered by peritoneum (at) or totally covered by peritoneum (above). Areas covered by peritoneum are inspected for serosal penetration and, if apparent, are sampled separately by four blocks. The retroperitoneal aspect should be painted by the locally preferred method – Leeds General Infirmary use 100% ethanol, dabbed dry with tissue paper and then painted with India ink (Windsor & Newton). This should be dabbed dry with tissue paper and then painted with acetic acid. This process will leave a dense black deposit on the specimen. This procedure is important as it rules out false positive involvement of the circumferential resection margin caused by poor embedding and sectioning. The distance from level of the middle of the tumour to the high tie and to each margin should be measured.

The specimen should be well fixed prior to cutting. The site of the tumour is sliced at 0.3-0.5cm intervals, including up to 2cm above and below, and laid out on a flat surface in good light for macroscopic inspection. The slices of the tumour are then laid out in order and photographed with a cm scale in the photograph and a 2cm x 2cm colour digital slide is produced. Both the 2 macroscopic and the sliced tumour colour digital slides should be sent/emailed to the EnROL Trial Office, labelled with the hospital, surgical number and trial number.

The quality of surgery of rectal cancer specimens should be commented on using the CRO7 scale for the mesorectum and the anal canal as described below.

## Grading of rectal cancer specimen

### Mesorectum

The macroscopic description should assess the quality of the mesorectum on the specimen. There are 3 grades:

**Grade 3** Mesorectal plane: Intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5mm. No coning on the specimen. Smooth CRM on slicing.

**Grade 2** 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 the insertion of levator muscles. Moderate irregularity of CRM.

**Grade 1** Muscularis propria plane: Little bulk to mesorectum with defects down onto muscularis propria and/or very irregular CRM.

### Anal Canal

**Grade 1** Perforation or dissection plane in wall of anal canal. The anal canal shows perforation of the tumour or bowel or the CRM is in the submucosa or muscularis wall.

**Grade 2** Sphincter muscle plane. Dissection plane is on the sphincter muscle.

**Grade 3** Levator plane. Dissection plane is outside the levators. The levators are applied to the specimen forming a cylindrical specimen.

The extent of the tumour involvement of the perirectal tissue is assessed with particular attention being paid to the circumferential resection margin (CRM). The maximum extent of tumour spread (called 'extent') from the outer limit of the muscularis propria is measured by ruler, this should be to the edge of tumour spread at the greatest distance of penetration from the muscular wall, be it direct, discontinuous, vascular or lymph node involvement. The smallest distance of the tumour from the circumferential margin will then be measured. Area(s) of involvement can usually be seen by naked eye and any suspicious area should be sampled for histology. Four blocks should be taken of the CRM. If the tumour is situated in the rectum and occupies the anterior quadrant this should be stated. The presence of perforation should be identified.

The specimen is now turned over such that the mucosal aspect faces downwards and the retroperitoneal/mesenteric face is upwards. The C2 node nearest to the main vascular tie is identified and

sampled, and the whole of the specimen from the vascular margin, i.e. that nearest the surgical ligature of the inferior mesenteric artery, down to the area of the removed tumour segment, is serially sliced down to the external aspect of the muscularis propria. Similarly, the segment of the rectum below the tumour is also serially sliced. Whilst incising the mesentery and mesorectum, lymph nodes and tumour deposits should be identified and sampled. Metastases and lymph nodes adjacent to the circumferential margin should be sampled en bloc with the resection margin which has been identified by painting with India ink.

Lymph nodes greater than 0.5cm distance from the circumferential resection margin or present in the mesentery of the sigmoid colon may be sampled in a routine fashion. Those <0.5cm from the CRM should be taken where possible with the CRM. The distal resection margin should be sampled for tumour involvement.

**Lymph nodes**

Any metastatic deposit >3mm (TNM5) will be recorded as a lymph node and the number of these lesions recorded on the form. Only half of the lymph nodes will be embedded. As many lymph nodes as possible should be found. The C2 node is the node of the high tie closest to the tumour.

**Histology**

Levels on a block may be required if tumour is close (<5mm) to a margin. Involvement is defined as tumour 1mm or less away from the inked margin. Accurate measurement of the minimum distance between tumour and the circumferential resection margin should be performed by microscopy on the haematoxylin and eosin stained slide using the Vernier scale on the microscopic stage or using graph paper photocopied onto acetate. Shrinkage of tissue may occur during processing but this does not materially affect the accuracy of this measurement as long as it is consistently performed at the same stage in the process, i.e. on the microscopic slide. Assessment by microscopy is required as a florid peri-tumoural inflammatory reaction or fibrosis will lead to an overestimate of macroscopic extent of tumour spread, and other microscopic deposits may be detected. Macroscopic measurements are accurate enough for the distance from the muscular wall to the edge of the tumour as this measurement is only used when comparing the extent of spread/size of tumours. Peritoneal involvement is said to exist when tumour cells have penetrated through the serosal membrane or are seen on the surface enmeshed in a fibrinoid inflammatory reaction. Four blocks of areas suspicious of peritoneal involvement should be taken. Levels may be necessary if definite peritoneal involvement is not shown. Extramural vascular invasion should be looked for and may require EVG staining. This is one of the most under-reported areas and you should aim for >30% of cases showing EMVI.

## Method for dissection of colonic carcinoma specimens

Colonic specimens differ in that only caecal and lower sigmoid tumours may have a significant retroperitoneal aspect. With colonic specimens the most important parameters are distance to proximal and distal margins, distance of tumour from nearest C2 node at the surgical mesenteric margin, and peritoneal involvement. If the tumour is sited equidistant between the high ties then two C2 nodes should be taken and the shorter distance entered on the form. The distance should be measured from the middle of the tumour to the vascular tie. It is still valuable to measure the extent of spread from the muscularis propria. The distance of tumour from the retroperitoneal circumferential margin is only really important in low sigmoid and caecal tumours. If the tumour is adjacent to a retroperitoneal margin, this measurement should be made. The photographs are still important as they provide a good record of the quality of the resections and extent of tumour spread.

**PLEASE NOTE**

As well as the 3 macroscopic photographs/digital slides, either the original diagnostic sections, which will be copied and then returned to the relevant participating hospital, or a second set of haematoxylin and eosin sections, should be sent to the EnROL Trial Office. Central review of the photographs and histology will be performed to audit the surgeon/pathology. Pathologists should indicate by marking the slide which haematoxylin and which eosin slide is diagnostic of CRM involvement or peritoneal involvement if it is present.

It would be appreciated if two extra pieces of tumour and one extra piece of normal mucosa could be taken and blocked. These should be sent with the photographs to the EnROL Trial Office. This would enable an archive of colorectal cancer to be started which could subsequently be used for molecular or immunohistochemistry studies. Use of this material would be open to all pathologists participating in the EnROL Trial.

## APPENDIX 2: ASSESSMENT OF COMPLICATIONS

The definitions below have been modified from Lang et al [24] who reported a doubling of cost and hospital stay associated with postoperative complications.

### Cardiorespiratory

- Respiratory failure (requiring mechanical ventilation)
- Cardiac failure, cardiac index < 2 litres per $m^2$ (treated first by fluid resuscitation and if no response by inotropic of vasoconstrictive medication)
- Pulmonary oedema (radiological diagnosis)
- Arrhythmia (ECG changes requiring medical treatment and/or electroconversion)
- Pleural fluid (radiographic diagnosis)
- Acute myocardial infarction (electrocardiographic diagnosis)
- Acute renal failure (requiring haemofiltration)
- Stroke with neurological symptoms
- Pulmonary embolism
- Distal ischaemia
- Deep vein thrombosis (requiring duplex or radiological or other confirmation)
- Other cardiorespiratory

### Surgical

- Unexpected blood loss >0.5 litres during operation
- Bowel perforation
- Ureteric damage
- Wound dehiscence – involving separation of deep closure
- Postoperative bleeding (overt blood loss requiring > 2litre transfusion with normal clotting profile)
- Delayed oral intake (intravenous fluids > 1 week owing to postoperative ileus)
- Bowel obstruction requiring reoperation
- Anastomotic leakage – defined[25] within 30 days of surgery radiologically (demonstration on abdominal CT with oral contrast, MRI or by contrast enema), surgically (visual evidence of faecal leakage at relaparotomy) or at autopsy (presence of a disrupted anastomosis).
- Necrosis of stoma (requiring surgery)
- Aspiration Pneumonia (radiological diagnosis with appropriate history)
- Other surgical

### Infective

- Sepsis (pyrexia > $38^0$ septic focus or positive blood culture)
- Postoperative peritonitis (clinical diagnosis)
- Abdominal abscess (ultrasonograpy, computed tomography or operative diagnosis)
- Necrotising fasciitis
- Wound infection - defined as any one of the following (modified from reference 26)

1. Purulent discharge or the aspiration of pus

2. Erythema or localised swelling requiring antibiotics or surgical drainage, unless the drainage is clear and negative on culture i.e. a seroma
3. A diagnosis of a wound infection made by a doctor.
4. Report of wound discharge by the patient unless it is proven to be uninfected

- Chest infection (radiological diagnosis or empyema)
- Urinary tract infection
- Disseminated intravascular coagulation
- Other infective complication

Major morbidity is defined as haemorrhage (requiring transfusion), any re-operation or readmission, anastomotic leakage, wound dehiscence, sepsis requiring at least high dependency support, HDU stay of > 5 days, unplanned admission to Intensive or Coronary Care Unit and death – when any one of these occur within the hospital admission or 30 days of surgery.

## APPENDIX 3: DATA REQUIREMENTS

### Data required prior to randomisation

At randomisation the following information will be required:

- patient's initials, date of birth, gender
- for patients who have consented to provide this information: patient's full name, NHS number and ethnicity
- surgeon's name
- eligibility criteria fulfilled
- written informed consent obtained from the patient
- site of tumour (colon or rectum definition: at or within 15 cm of anal verge on rigid sigmoidoscopy with the patient awake)
- estimated date of surgery
- surgeon's confidential email address (or fax number) for notification of treatment allocation

### Data required prior to surgery

- information about the consent process including name of person taking consent, version of consent documents used, details of consent to optional items, if GP letter sent
- date of diagnosis
- height and weight
- number and type of previous abdominal operations
- details of any preoperative radiotherapy – short course; long course. [NB long course chemoradiotherapy for a probable T4 rectal carcinoma is an exclusion criterion – see 5.2]
- distance in cm from the anal verge for rectal cancer
- blood transfusion requirements in the 7 days before operation (no. units)
- full blood count, urea, creatinine, electrolytes, liver function tests within 7 days before operation
- other data required for P-POSSUM[27] scoring
- presence or absence of metastatic disease and site/s (peritoneal; lung; liver; other)
- presence or absence of any other malignancy (excluding basal cell carcinoma, in situ carcinoma of cervix or prostate cancer) within the preceding 5 years
- Health Economics, Fatigue, Quality of Life and Body Image Scale questionnaires to be completed with the Research Nurse, along with measurement of standardised performance indicators, within 4 weeks before surgery (can be done between consent and randomisation).

### Data required at surgery

- Surgeon's name
- the ASA physical status classification:

  ASA 1- Normal healthy patient
  ASA 2 - Patient with mild systemic disease with no functional limitations
  ASA 3 - Patient with moderate systemic disease with functional limitations
  ASA 4 - Patient with severe systemic disease that is a constant threat to life
  ASA 5 - Moribund patient who is not expected to survive another 24 hours with or without surgery
- date of operation
- type of resection (laparoscopic or open)
- description and mode of operation

- other operative procedure/s undertaken
- blood loss
- intraoperative complication/s
- duration of operation
- health economics information on equipment used
- site, length and type of incision/s (abdominal incisions only)
- type of stoma, if applicable
- presence of non contiguous intraabdominal cancer
- surgeon's assessment as to whether local removal of the tumour was complete
- surgeon's assessment of whether the procedure was curative
- the reason for conversion in laparoscopic procedures - Conversion is defined as the inability to complete the dissection fully laparoscopically, including the vascular division, and it usually, but not always, requires the use of a larger incision than that needed to remove the specimen.
- the extent of anatomic nerve preservation in total mesorectal excision
- operative severity scoring for P-POSSUM
- details of epidural use
- timings of operation
- If overnight stay in HDU required
- theatre personnel present
- equipment used

### Data required 3 days post-surgery

- Assessment of compliance with Enhanced Recovery Programme

### Data required within 30 days of surgery or during the hospital stay if > 30 days

- Postoperative hospital stay (no. days)
- Readmission within 30 days of operation, and date of readmission if applicable
- Reoperation within 30 days of operation and details of operation
- Postoperative complications (see Appendix 3)
- Time in HDU or ITU and whether it was a readmission
- Duration of intravenous infusion (hours)
- Time to first bowel movement (days)
- Fluid balance within the first 3 days
- Use of analgesics and patient reported pain scores within the first 3 days
- Whether blinding was maintained, if not reason why not
- SPIs at 4 weeks postoperatively
- Questionnaires to be completed 4 weeks postoperatively for Fatigue, QoL and health economics, which will be sent by post, or given to the patient if they are attending a convenient clinic, if the patient has left hospital
- Patient Operation Experience and Staff Blinding Experience questionnaires completed at day 1 and day of discharge/day 7

### Data required between 30 days and 6 months following surgery

- Details regarding re-admission and reoperation: date, type, length of hospital stay including ITU & HDU, indication, description of re-operation(s)

- Administration of chemotherapy: date, type, duration
- Administration of radiotherapy: date, dose and duration
- Recurrence – If yes recurrence form to be completed
- SPIs at 3 and 6 months postoperatively
- Questionnaires to be completed at 3 and 6 months postoperatively for Fatigue, Health Economics and QOL, and at 6 months only questionnaire for cosmetic assessment to be sent by post or given to the patient at the appropriate time.

### Data collected at 12 months postoperatively

- Date of review
- Recurrence - if yes, recurrence form to be completed.
- Incisional hernia - if yes, if operation was necessary
- Admission with adhesion obstruction - if yes, if operation was necessary
- Presence or absence of a stoma
- Questionnaire to be sent for cosmetic assessment

### Data to be collected if recurrence occurs

- Date of recurrence
- Site: Lung / Liver / Peritoneal / Locoregional / Laparotomy wound / Perineal wound / Port site wound / Extraction site wound / Other
- Method of diagnosis
- Treatment if recurrence – curative/ palliative

### Data to be collected on death

- Date of death
- Cause of death
- Presence of colorectal cancer at death

## Time points for data submission

| eCRF | Data Collection Time Point | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre Operative | At Surgery | Day 3 | 2 weeks | 4 weeks | 3 month | 6 month | 12 month | As required |
| Randomisation | X | | | | | | | | |
| Consent Notification | X | | | | | | | | |
| Data Pre Surgery [B] | X | | | | | | | | |
| Data At Surgery | | X | | | | | | | |
| Intra-Operative Assessment | | X | | | | | | | |
| ERP Compliance | | | X | | | | | | |
| Data within 30 days post op [B] | | | | | X | | | | |
| Pathologist Form | | | | X | | | | | |
| Follow Up (3 month) [B] | | | | | | X | | | |
| Follow Up (6 month) [B] | | | | | | | X | | |
| Follow Up (12 month) | | | | | | | | X | |
| Re-admission | | | | | | | | | X [A] |
| Recurrence | | | | | | | | | X |
| Notification of Death | | | | | | | | | X |
| [A] To be completed for all re-admission after discharge until 6 month post surgery. | | | | | | | | | |
| [B] Includes SPI data collected at this time point | | | | | | | | | |

| Questionnaire | Data Collection Time Point | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre Operative | At Surgery | Day 3 | 2 weeks | 4 weeks | 3 month | 6 month | 12 month | As required |
| MFI-20 | X [B] | | | | X | X | X | | |
| SF-36 | X [B] | | | | X | X | X | | |
| EQ-5D | X [B] | | | | X | X | X | | |
| Health Economics | X [B] | | | | X | X | X | | |
| Body Image | X [B] | | | | | | X | X | |
| [B] to be completed not more than 4 weeks prior to surgery | | | | | | | | | |

## APPENDIX 4: PATIENT INFORMATION SHEET

*To be printed on hospital headed paper*

EnROL – Enhanced Recovery Open versus Laparoscopic

**Patient Information Sheet** V4.0_25Jan2011

Title: Multicentre study of conventional versus laparoscopic surgery for colorectal cancer within an Enhanced Recovery Programme

You are being invited to take part in a clinical research study comparing two different approaches to surgery for bowel cancer within an enhanced recovery programme. Before you decide it is important for you to understand why the research is being done and what it will involve. Your doctor and/or nurse will discuss the study with you and allow you time to ask any questions you may have. This information sheet is designed to help you understand what the study is about and you may take this sheet away with you. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**Taking part in this study is entirely voluntary.**

### Why Is This Study Being Done?

Operations for bowel cancer are usually carried out by conventional open surgery through an abdominal incision. The recent development of specialist instruments has made it possible to carry out this type of operation laparoscopically (keyhole surgery) providing equivalent cancer cure rates to those of open surgery. Laparoscopic surgery involves putting narrow tubes into your abdomen through which special instruments can be used to carry out the operation. The surgeon uses a small camera to watch on a television screen exactly what is going on inside your abdomen during the operation. In laparoscopic surgery, the cut needed to remove the bowel cancer is much smaller than that needed for the open or conventional operation. Although the laparoscopic operation may take a little longer than the conventional open approach, it may have the benefit of reducing the time you need to stay in hospital and enable you to return to work or your normal activities more quickly and reduce the risk of developing complications.

### What is an Enhanced Recovery Programme?

In this trial we are comparing the newer laparoscopic surgery with the standard open surgery to see if it is at least as safe and effective. We also believe that the conventional way of caring for you before, during and after your bowel operation can be improved in a number of ways. This is called an enhanced recovery programme and aims to improve your recovery in the following ways

1. Providing you with extra nourishing drinks before and after your operation.
2. Using different ways of relieving pain following your operation such as an epidural (a pain killing injection into your back) and painkilling tablets.
3. Early removal of any surgical tubes such as urine catheters (a plastic tube in your bladder to measure your urine) and drips (tubes to give you fluid whilst you are not drinking) after your operation.
4. Encouraging early activity and exercise after your operation (staff will help you start standing and walking earlier after your operation).

All of the above treatments and procedures have been used before. Their combination may help you recover more quickly from your operation and enable you to return to normal daily activities following your operation sooner than you would otherwise have done.

### Why have I been chosen?

Your doctors will have explained that you need an operation to remove a bowel cancer.

We are inviting patients with bowel cancer at several different hospitals throughout the UK to join the trial. We need to study 266 patients like you.

## Do I have to take part?

You will be given time to consider taking part in the study. **Participation in the trial is entirely voluntary.** Your standard of care will not be affected if you decide not to take part in this study.

If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason. This will not in any way affect any future care you will receive from your medical and nursing team.

## What will happen to me if I take part?

In order to compare the standard open surgery with the newer laparoscopic surgery we need to randomise patients to receive one of the treatment options. Randomisation means that neither you nor your doctor will be able to select which treatment you will receive. The EnROL Trial Office in Oxford will use a computer to allocate you to one of the two surgery groups with equal chances of each surgical approach being the one you will receive. This will ensure that the number of patients in each of the two surgery groups is similar. The randomisation process means that you have a 1 in 2 chance (50%) of receiving laparoscopic surgery or standard open surgery.

If you agree to take part in the trial, having read and understood this information sheet and had any questions answered, you will be asked to sign a consent form to confirm your agreement. You will be given a copy of the consent form to keep along with this information sheet.

We will then contact the EnROL Trial Office to randomise you to one of the two surgical approaches. This will determine which form of surgery you will receive.

Either Laparoscopic (or 'keyhole surgery')

Or Open (or conventional) surgery.

Which ever surgical approach you have, the operation will be the same and the bowel cancer will be removed and you will be part of an enhanced recovery programme. If you are selected to have your operation carried out laparoscopically, but during the operation the surgeon is not happy that the laparoscopic approach is the best and safest thing for you, he will change the approach to a conventional open operation.

You and the ward staff will not know whether you had laparoscopic or open surgery until one week after the operation. Only the surgeon and theatre staff will know. The wound will be covered with an opaque dressing until one week after the surgery. The reason for this is that if the ward staff know what type of operation was undertaken then it may alter the way they treat you. This would then affect the result of the trial and we will not find out if there is a difference between the treatments. If there are any complications with the wound, the dressing will be removed and you will receive the appropriate treatment.

If you decide to take part in the trial you will need to attend hospital appointments at 2 weeks, 4 weeks, 3 months and 6 months after your surgery. You would usually have appointments around 2 weeks and then at 3 and 6 months after surgery for bowel cancer although this does vary between hospitals, so if you choose to be part of the trial you will have an extra visit to the hospital 4 weeks after your operation.

After your surgery tissue samples from the tumour will be assessed in a standard way by your hospital's pathologist, as they would be for any patient having a bowel cancer removed. In addition your tumour will also be assessed by another pathologist from outside your hospital. This will be done to check that this assessment is being done consistently for all of the patients in the trial.

## What will I have to do to take part?

If you decide to take part in the trial you will be asked to complete some questionnaires about how you feel and provide information about your use of healthcare facilities - such as GP surgery visits, as well as home and District Nurse visits. You will be asked to complete questionnaires before your operation, and then either at your out-patient appointments or by post with a stamped addressed envelope, at 4 weeks and at 3 and 6 months following surgery. At the same time we will ask you to perform some simple exercises called Standardised Performance Indicators (SPIs) which take about 5 minutes to measure and involve testing your balance, walking and getting up from a sitting position.

The day after surgery and again before you are discharged you will be asked a few questions about what type of surgery (open or keyhole) you think you have had.

At one year after surgery we will also ask you to answer some questions regarding the cosmetic appearance of your abdomen. We may ask you to allow us to take a few extra blood samples to assess the effects of surgery on the body.

Your GP and any other doctors who may treat you will be notified that you are taking part in the study.

The data we obtain from the questionnaires is a very important part of this trial. It is therefore important that you understand that if you agree to participate that all of the questionnaires should be completed whenever possible so that the results of the trial are as robust as we can make them.

### What will happen to the results of the research study?

Results of the trial are likely to be published in medical journals, used for scientific presentations and may also be forwarded to health authorities worldwide. The confidentiality of all patients will be maintained and you will not be identified in any reports or publications resulting from the study. If you would like to have a copy of the published results, please ask your doctor.

### What are the possible disadvantages and risks of taking part?

We do not anticipate that there will be additional risks to you from taking part in this study and, in particular, research has demonstrated that laparoscopic surgery does not worsen cancer cure rates. Should you experience any difficulties within the first two weeks after leaving hospital we ask that you contact us for advice and help.

### What are the possible benefits of taking part?

The purpose of the trial is to find out how the newer laparoscopic or keyhole approach compares with conventional open surgery when all patients take part in the enhanced recovery programme. We expect that the enhanced recovery programme will allow you to leave hospital earlier than normal

Your participation in the study may help patients in the future by giving important information about whether the newer laparoscopic or keyhole approach is better, and whether we might recommend this approach and the enhanced recovery programme for the treatment of bowel cancer patients.

### What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the technique or treatment that is being studied. If this happens, your doctor will tell you about it and discuss whether you want to continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.

On receiving new information your doctor may consider it to be in your best interests to withdraw you from the study. Your doctor will explain the reasons and arrange for your care to continue.

### What happens if I change my mind during the study?

We would certainly recommend that you have your surgery, however, participation in the study is voluntary and you may leave the trial at any time without giving reasons and without affecting your future care.

### What if something goes wrong?

Because laparoscopic surgery and the enhanced recovery programme are still relatively new techniques, unexpected side effects may occur. You will receive the best medical care available during and after the trial and in the unlikely event of an injury arising from taking part in this trial, you will be provided with the necessary care.

If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Oxford (in respect of any harm arising out of the participation in the Clinical Trial) or the NHS (in respect of any harm which has resulted from the clinical procedure being undertaken). Your doctor will give you further information if necessary.

### Blood, urine and tissue samples

The EnROL trial gives us an opportunity to perform tests on tissue, urine and blood samples that may give us extra information on the effects of surgery, the effects of treatment following surgery and even why some people develop cancer in the first place. If you agree to join the trial you will be asked if you would consent to donate a few extra samples of your blood (maximum 105 ml of blood, equal to 7 tablespoons) and urine and some of the tissue that will be removed during your surgery.

This part of the trial is optional so you can be part of the trial but not agree to donate these samples, or you can agree to donate just some of the samples.

**Tissue**

Scientific advances mean that we are constantly finding new tests that we can apply to the cancer tissue that was removed at the time of surgery. These tests might tell us which cancers are more likely to respond to chemotherapy, or what causes some cancers to spread or grow more quickly than others. It is not possible to give a complete list of the tests we will perform because as our scientists discover more about cancer, we will be able to try new tests. This is because we can store the cancer tissue for many years and use only tiny fragments for the lab tests. It is likely that some of the cancer tissue will be used for research with drug companies in the search for new treatments, which could lead to commercial gain for the company. When you consent to let us use your tissue for research, we would like to make it clear that you would not be entitled to any financial gain.

**Blood**

We would like to take a few extra blood samples which we will use to look at factors in your blood to see if these are related to your recovery from surgery and to examine the effects of the surgery on the immune system and see if those effects differ depending on whether the surgery is open or laparoscopic.

Blood samples may also be used to isolate your DNA. DNA is the chemical that makes up genes, the factors that we inherit from our parents that determine our characteristics (height, hair colour, appearance etc). There is growing evidence that we can also inherit an increased chance of developing certain diseases, including cancer. Scientists who are experts in genetics would like to perform tests on the DNA collected from your blood – these could give us information on which genes might cause cancer, or increase the chance of side effects from chemotherapy.

This science is changing rapidly and, like the tissue tests, we would like permission to use new tests, when they appear in the future.

**Urine**

We would like to collect urine samples for use with the blood samples to look for factors that may be related to your recovery from surgery and your cancer.

We will store the tissue, urine and blood in a central laboratory using a code, not your name, to identify the sample. We set up a small committee of scientists and doctors to make sure that the tissue and blood (DNA) will only be made available to researchers working to the highest ethical standards. Samples are kept indefinitely for use in future research projects and their continued storage is reviewed on an annual basis. When they are no longer useable they are destroyed. In the trial we will be monitoring your treatment and progress, and we can use the code to link the tissue/blood samples to the information that we collect during the trial. However, we will keep you anonymous and the researchers working with your tissue/blood will not know your name.

## Who is organising and funding the research?

The study is being organised by the Oncology Clinical Trials Office in Oxford and jointly sponsored by the University of Oxford and the North West London Hospitals NHS Trust. Funding for the trial is provided by The Bobby Moore Fund, Cancer Research UK.

## Who has reviewed the study?

The study has been independently reviewed by Cancer Research UK. The Oxford Research Ethics Committee B, one of 13 national research ethics committees, has given its approval (reference number 07/H0605/150), along with your hospital Trust.

## Will taking part in the study be confidential?

The information that you provide during the trial by completing the questionnaires and the information collected about you will be kept at the EnROL Trial Office, which is part of the University of Oxford. This information is strictly confidential.

If you agree, information held by the NHS and records maintained by The NHS Information Centre may be used by the EnROL Trial Office to keep in touch with you and to follow up your health status. This requires

your name and NHS number to be recorded at the EnROL Trial Office. This information would be collected once only and then retained securely and only accessed by authorised personnel.

To obtain information from The NHS Information Centre we will need to provide the Medical Research Information Service (MRIS) at The NHS Information Centre with some information (such as your name and NHS number) but we would like to assure you that any data sent to MRIS will be encrypted to protect your identity.

We would also like your permission to use anonymised data obtained from the questionnaires you will complete in future research projects including those carried out by researchers outside the University of Oxford. Where required ethical approval will be obtained for such projects.

Occasionally, at any time during or after the study, your doctor, or the EnROL Trial Office staff (University of Oxford – the sponsor) will be allowed access to your medical records. This is so that we can check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site, other than to MRIS as described above. Once we have collected your name and NHS number any other information that leaves the hospital will have your name and address removed so that you cannot be recognised from it. If data is to be sent to other groups in the UK or abroad we will not include information that identifies you by name (only your trial number will be used) and agreements will ensure that the data is treated confidentially.

### What if I have more questions or haven't understood something?

Please feel free to ask any further questions of the doctors and nurses looking after you before deciding to take part in the trial or at any time during the study.

If you would like further information about clinical trials, it is available at the following website, however please bear in mind that as this trial is not testing drugs but comparing the two different types of surgery not all the information on the website is relevant to this trial. :

http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Clinicaltrials/Understandingtrials/Understandingtrials

## Thank you for reading this information sheet.

Your local contact is:

Independent contact is:

## APPENDIX 5: CONSENT FORMS

***To be printed on hospital headed paper***

EnROL – Enhanced Recovery Open versus Laparoscopic

**Patient Consent Form A: Study Participation**

**Title:** **Multicentre study of conventional versus laparoscopic surgery for colorectal cancer within an Enhanced recovery Programme**

ISRCTN48516968 EudraCT 2007-005243-13

Oxford Research Ethics Committee B, (reference number 07/H0605/150) Consent Form A v3.0_06Nov2009

| | | | | | |
|---|---|---|---|---|---|
| **Study Surgeon Name:** | | | **Study Site:** | | |
| **Patient Name:** | | | | | |
| **Relating to Patient Information Sheet** | **Version No.:** | | **Version Date:** | ___/___/_____ | |

**Patient Statement and Signature** *to be completed by the patient*

Please **initial** the boxes below if you agree

| | |
|---|---|
| 1. I confirm that I have read and understand the EnROL Patient Information Sheet. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. | |
| 2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason and without my medical care or legal rights being affected | |
| 3. I give my permission for information held by the NHS and records maintained by The NHS Information Centre to be used to keep in touch with me and follow up my health status | |
| 4. I also understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the EnROL Trial Office (University of Oxford, Sponsor), from regulatory authorities and other designated individuals working on the trial where it is relevant to my taking part in the research. I give permission for these individuals to have access to my medical records | |
| 5. I understand that I will not be identified in any reports or publications resulting from the study | |
| 6. I agree to the use of anonymised data obtained from my completed questionnaires in future projects, including those carried out by researchers outside of the University of Oxford | |
| 7. I give my permission for a letter and information about the EnROL trial to be sent to my General Practitioner (GP), which will tell him/her of my participation in the study | |
| 8. I agree to participate in this study | |

My signature confirms that I have had an opportunity to ask questions, and all of my questions have been answered. [You will be given a signed and dated copy of this consent form to take away with you]

| | | | | | |
|---|---|---|---|---|---|
| **Patient signature:** | | **Name (print):** | | **Date signed:** | ___/___/_____ |

**Investigator Statement and Signature** ***To be completed by the person taking consent***

I have discussed this clinical research study with the patient and/or his or her authorised representative using a language that is understandable and appropriate. I believe that I have fully informed the participant of the nature of this study and the possible benefits and risks of taking part. I believe the participant has understood this explanation.

| | | | | | |
|---|---|---|---|---|---|
| **Signature:** | | **Name (print):** | | **Date signed:** | ___/___/_____ |

*To be printed on hospital headed paper*

# EnROL – Enhanced Recovery Open versus Laparoscopic

## Patient Consent Form B: Blood, Urine & Tissue Sample Collection and Storage

| | | | | | |
|---|---|---|---|---|---|
| **Study Surgeon Name:** | | **Study Site:** | | | |
| **Patient Name:** | | | | | |
| **Relating to Patient Information Sheet** | **Version No.:** | | **Version Date:** | __ / ___/_____ | |

Oxford Research Ethics Committee B, (reference number 07/H0605/150) Consent Form B_v3.0_06Nov2009

**Patient Statement and Signature** ***to be completed by the patient***

Please **initial** each box below if you agree with the corresponding statement

| | |
|---|---|
| 1. I confirm that I have read and understand the EnROL Patient Information Sheet. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily | |
| 2. I agree to give a sample of blood (105 ml) for research in this project. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without giving a reason and without my medical treatment or legal rights being affected | |
| 3. I agree to donate a sample of my tissue removed at the time of my surgery for research in this project. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without giving a reason and without my medical treatment or legal rights being affected | |
| 4. I agree to give a sample of urine for this research project. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without giving a reason and without my medical treatment or legal rights being affected. | |
| 5. I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test | |
| 6. I know how to contact the research team if I need to, and how to get information about the results of the research | |
| **Consent for storage and use in possible future research projects** | |
| 7. I understand that I am gifting the blood, urine and tissue samples to The University of Oxford. The University of Oxford will be a custodian of the samples and will coordinate the usage of samples for research by the EnROL Trial Management Group in accordance with Ethics approval. | |
| 8. I agree that the samples I have given and the information gathered about me can be stored by the University of Oxford (who is co-sponsoring the trial with North West London Hospitals NHS Trust and acting as custodian of the samples) for possible use in future projects, as described in the attached patient information sheet. I understand that some of these projects may be carried out by researchers other than the University of Oxford, including researchers working for commercial companies | |
| **Consent for genetic research** | |
| 9. I understand that this project and future research may include genetic research on the sample given, aimed at understanding the genetic influences on colorectal cancer and the treatment of colorectal cancer but that the results of these investigations are unlikely to have any implications for me personally | |
| 10. I voluntarily agree to participate in this part of the study | |

My signature confirms that I have had an opportunity to ask questions, and all of my questions have been answered satisfactorily. [You will be given a signed and dated copy of this consent form to take away with you]

| | | | | | |
|---|---|---|---|---|---|
| **Patient signature:** | | **Name (print):** | | **Date signed:** | ___/___/_____ |

**Investigator Statement and Signature** ***To be completed by the person taking consent***

I have discussed this clinical research study with the patient and/or his or her authorised representative, using a language that is understandable and appropriate. I believe that I have fully informed the participant of the nature of this study and its possible benefits and risks and I believe the participant understood this explanation.

| | | | | | |
|---|---|---|---|---|---|
| **Signature:** | | **Name(print):** | | **Date signed:** | ___/___/_____ |

## APPENDIX 6: GP LETTER

*To be printed on hospital headed paper*

Dear Dr

RE: **EnROL - Multicentre study of conventional versus laparoscopic surgery for colorectal cancer within an Enhanced Recovery Programme**

Patient name: Date of Birth:

Address: Trial number:

The above patient has been entered into the EnROL trial. The trial is comparing laparoscopic versus open surgery within an Enhanced Recovery Programme.

Early research has suggested that the laparoscopic technique may shorten recovery. Because laparoscopy is more costly and also operative time is slightly greater, we need to compare it with conventional open surgery when perioperative care has been optimised within this programme. An enhanced recovery programme involves addressing a number of pre and post operative factors such as ambulation, analgesia, gastrointestinal function, immuno-suppression, nutrition and stress responses. We believe that this programme will enhance recovery significantly.

The main difference you will notice is that patients will be well enough for discharge from hospital earlier than previously – even as early as 3 days following surgery in certain cases. Time to full recovery may also decrease and will probably average 3 to 4 weeks. A Patient Information Sheet is enclosed to provide further information regarding the study.

This trial should not involve input from yourself or your staff over and above the standard care given to patients post surgery. If there are problems within two weeks of surgery we ask patients to come directly to us.

**Your local contact for this patient's care is:**

**Name:** **Telephone:**

If you have any enquires regarding this trial please feel free to contact the EnROL Trial Office on:

Tel: 01865 617017 Fax: 01865 617010 E-mail: enrol@octo-oxford.org.uk

Many thanks for your help and co-operation with this study.

Yours sincerely,

(EnROLGPLetterv2.0_21Jan2008)

## APPENDIX 7: CONSENT WITHDRAWAL FORM

***To be printed on hospital/Trust headed paper***

EnROL – Enhanced Recovery Open versus Laparoscopic

**Consent Withdrawal Form**

**Multicentre study of conventional versus laparoscopic surgery for colorectal cancer within an Enhanced Recovery Programme**

ISRCTN48516968 EudraCT 2007-005243-13 Consent Withdrawal Form v2.0_25Jan2011

Oxford Research Ethics Committee B (reference number 07/H0605/150)

| | | | |
|---|---|---|---|
| **Study Doctor Name:** | | **Study Site:** | |
| **Patient Name:** | | **Trial No.:** | |

| **Patient Statement and Signature** | ***To be completed by the patient*** | |
|---|---|---|
| | | **Please initial the boxes below if you agree** |
| 1. | I wish to withdraw from further study treatment and follow-up related to the trial named EnROL. I understand that withdrawing from the study will not affect my medical care or legal rights. | |
| 2. | I understand that data collected prior to this date may still be used by responsible individuals taking part in the research. | |
| 3. | I understand that any tissue samples and blood samples collected before the date of this consent withdrawal form belong to the sponsor and will be used anonymously according to its intended use for the trial and any future sub-studies they were collected for and consented to. | |
| 4. | I wish to withdraw consent to providing further tissue and blood samples. | |
| 5. | I understand that my medical records will still be subject to audits and inspections by the sponsor and regulatory bodies solely for the purpose of auditing data related to this trial collected prior to this date. | |
| 6. | I no longer permit any new information from my medical records to be used to obtain information for this study, unless it is used specifically to assess any safety concerns related to my participation in the trial. This will apply for all records made on or after the date of this form. | |
| 7. | I allow information held about my progress at the Medical Research Information Service, NHS centre for Health and Social Care to be followed up by the trials office and understand that this will not involve any direct contact with me from the trials team. | |
| 8. | The Investigator has discussed the withdrawal from the clinical research study with me, using a language that is understandable and appropriate. I have had the opportunity to ask questions. | |
| 9. | I understand that my doctor will need to notify the EnROL Trial Office of my withdrawal. | |

| | | | | | |
|---|---|---|---|---|---|
| **Patient signature:** | | **Name (print):** | | **Date signed:** | ___/___/_____ |

**Investigator Statement and Signature** ***To be completed by the person taking consent***

I have discussed the withdrawal from the clinical research study with the patient, using a language that is understandable and appropriate. The patient has had the opportunity to ask questions.

| | | | | | |
|---|---|---|---|---|---|
| **Signature:** | | **Name (print):** | | **Date signed:** | ___/___/_____ |

**The completed Consent Withdrawal Form must be kept in the EnROL Investigator Site File, a copy given to the patient and a copy filed in hospital notes**

OCTO must be informed in writing of consent withdrawal by submission of a Consent Withdrawal Notification Form on the EnROL eCRF website. This Consent Withdrawal Form must **not** be sent to OCTO.

## APPENDIX 8: DISCHARGE INFORMATION LEAFLET FOR PATIENTS

### ENHANCED RECOVERY PROGRAMME

### DISCHARGE INFORMATION LEAFLET NO 1

### Things to look out for

This leaflet describes things that you need to be aware of after you leave hospital. Complications should not happen very often, but it is important that you know what to look out for. If you are worried about any of the following things during the first two weeks after surgery, please phone the telephone numbers on this leaflet first, not your GP. If you cannot contact the people listed, then ring your GP.

### Your wound

It is not unusual for the wound to be slightly red and to be uncomfortable during the first 1-2 weeks. Please let us know if your wound is:

a) Becoming inflamed, painful or swollen.
b) Starts to discharge fluid.

### Your bowels

Your bowel habit may alter after removal of part of the bowel and may become loose or constipated. Make sure you eat regular meals 3 or more times a day and take regular walks during the first two weeks after your operation. If constipation lasts for more than 3-4 days then taking a laxative is advised. If you are passing loose stools more than 3 times per day for more than 4 days we advise taking medication such as Loperamide, Lomotil or Codeine phosphate.

### Passing urine

Sometimes after bowel surgery you may experience a feeling that the bladder is not emptying fully. This will usually resolve with time but if it does not or there is excessive stinging when passing urine, (suggesting infection) then please ring us.

### Abdominal pain or a temperature

It is not unusual to suffer griping pains during the first week following removal of a portion of the bowel. The pain usually lasts for up to a few minutes and will go away completely in between spasms.

Severe pain that lasts for several hours may indicate leakage of fluid from the area where the bowel has been joined together. This is rare but can be a serious complication. Should it occur it may be accompanied by a fever. On occasions though, leakage may occur which causes a fever and makes you generally unwell, but without any pain.

**If severe pain is lasting more than 1-2 hours or you have a fever and feel generally unwell, then you should contact us within a few hours on the telephone numbers provided.**

**9am – 5pm Mondays – Fridays:**
**……. (Colorectal Specialist Nurse)**
**Tel: ……..**

**Other times:**
**…….**
**Tel:……..**
**OR**
**Nurse in charge of Ward ……**
**Tel ……..**

## ENHANCED RECOVERY PROGRAMME

## DISCHARGE INFORMATION LEAFLET NO 2

This leaflet provides general information about diet, exercise, work, activities and driving.

### DIET

A healthy, varied diet is recommended and particularly eating meals 3 or more times a day. You may find that some foods upset you and cause looseness of the bowels. If that were the case you should avoid them for the first few weeks following your surgery. If you are finding it difficult to eat it is still very important to obtain an adequate intake of protein and calories. In that case we recommend that you should have 3-4 protein drinks a day to supplement your food. These can include all the protein drinks you tried prior to your surgery or Build-up, Complan etc. If you are suffering from diarrhoea then it is also important to replace the fluid loss and to drink extra liquid.

### EXERCISE

We encourage activity from day one following your surgery. You should plan to undertake regular exercise several times a day and gradually increase that during the 4 weeks following your operation until you are back to your normal level of activity. The main restriction we would place on exercise is that you do not undertake heavy lifting until 6 weeks following your surgery. In addition, if you are planning to restart a routine exercise such as jogging or swimming, that you wait until 2 weeks after surgery, and then start gradually. Common sense will guide your exercise and rehabilitation, in general if the wound is still uncomfortable, modify your exercise. Once the wound is pain free one can undertake most activities.

### WORK

Many people are able to return to work within 2-4 weeks following their surgery. If it involves a heavy manual job then we would not advise heavy work until 6 weeks' following surgery.

### DRIVING

It is advised that you do not drive until you are confident that you can drive safely. A good yardstick for this is when you have got back to most of your normal activities. Usually this will be within 2-4 weeks of surgery. It is important that pain has resolved sufficiently to enable you to undertake an emergency stop and turn the wheel quickly in an emergency, before you start driving again.

### HOBBIES/ACTIVITIES

In general it is advised that you take up your hobbies and activities as soon as possible again after surgery. It enables you to maintain your activity and also will benefit your convalescence. We would not advise restricting taking these up unless they cause significant pain or involve heavy lifting within the first 6 weeks following surgery.

**9am – 5pm Mondays – Fridays:**
**…… (Colorectal Specialist Nurse)**
**Tel: ……..**

**Other times:**
**…….**
**Tel:……..**
**OR**
**Nurse in charge of Ward ……**
**Tel ……..**

## APPENDIX 9: STANDARD OPERATING PROCEDURE (SOP) FOR SURGICAL PROCEDURES

The object of the SOP for surgery is to define the surgical technique thus ensuring consistency and quality control between centres.

The description of surgical methods is intended to be a comprehensive and detailed summary in order to avoid inconsistency which might affect credibility regarding the surgical techniques.

1. Surgeons should be able to undertake elective colonic or rectal resection resulting in positive resection margins of less than 7 and 12% respectively.
2. There should be sufficient experience that reoperation for haemorrhage occurs in < 3% of patients and reoperation for any reason, within 30 days of surgery, in < 15%.
3. Experience should encompass a minimum of 50 total mesorectal excisions (TME) and 100 laparoscopic colorectal resections prior to participation in the trial.
4. Vascular ligation of the bowel segment to be resected should preferably be undertaken early in the procedure but may be undertaken late, at the surgeon's discretion, provided the technique is recorded.
5. All energy sources used for dissection and vascular ligation should be used in such a way as to minimise inadvertent injury to other structures.
6. Contiguous organ involvement should be resected synchronously wherever possible, bearing in mind the exclusion criteria for enlisting patients in the EnROL Trial: section 5.2.
7. Anastomoses should be undertaken in bowel that is well vascularised, not under tension and using a conventional technique employing staples or sutures.
8. Operative technique should be recorded in the detail required by the trial management group.
9. Tumour cell dissemination should be minimised by minimal tumour handling.
10. Wounds should be protected from tumour cell contamination by techniques such as the use of a wound protector during tumour extraction, and a cytocidal liquid wash to wounds prior to wound closure.
11. A pneumoperitoneum should be established in such a way that there is minimal risk of inadvertent injury and when previous surgery has occurred close to the laparoscopic entry point, an 'open' or 'remote insufflation' technique should be used.
12. All wounds > or equal to 10mm should be closed surgically to minimise postoperative incisional herniation.
13. Prior to the start of the trial surgeons should have agreed they will follow these principles unless that would compromise the patient's safety, when the reason for variance will be recorded.

## APPENDIX 10: GUIDELINES FOR ANAESTHETIC CARE

The following principles should be adhered to:

1. Short acting anaesthetic agents should be used to facilitate the rapid emergence from anaesthesia.
2. A thoracic epidural should be placed at the appropriate level for the surgery. A postoperative infusion of local anaesthetic and opiate should be employed for 48 hrs.
3. Fluid management should be aimed at euvolaemia.
4. Long acting IV opiates should be avoided.

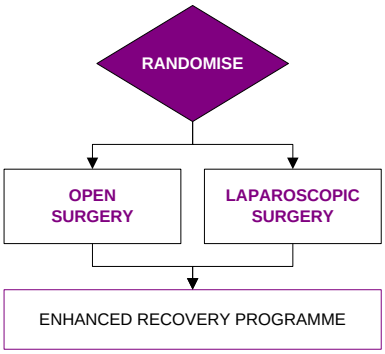
The following suggestions are from Dr Roger Kipling, Consultant Anaesthetist, Yeovil District Hospital who was the lead Anaesthetist for the Yeovil trial[14].

1. Remifentanil infusions with either sevoflurane or Propofol infusions provide excellent anaesthetic conditions and facilitate rapid emergence from anaesthesia while avoiding all the problems associated with longer acting opiates.
2. T8-9 thoracic epidurals perform well for open operations. A lower T10-11 approach allows for head down positioning during laparoscopic procedures and an additional caudal block is very useful for abdomino-perineal and some anterior resections.
3. In the absence of dehydration or bleeding, hypotension is invariably due to vasodilation and responds best to vasoconstriction rather than fluid infusion. This avoids the problem of fluid overload.
4. Fluid administration under these circumstances is usually 10-15 ml/kg/hr.
5. Oesophageal Doppler or Impedance Cardiography are useful non-invasive ways of assessing cardiac performance, and systemic vascular resistance in particular, during these resections.
6. It is quite possible to keep the patient at a normal temperature during long laparoscopic resections by using a hot air overblanket.
7. PEEP is useful during long periods of head-down positioning for laparoscopic resections

## APPENDIX 11: ENROL TRIAL SUMMARY

Conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme

**Chief Investigator:** Mr Robin Kennedy




### STUDY ENDPOINTS

**Primary:**
- Post-operative physical fatigue

**Secondary:**
- Post-operative hospital stay
- 30 day and in-hospital complications
- 30 day re-admission & re-operation rates
- Assessment of health economics using cost-effectiveness & cost utility
- Patient reported and functional outcomes
- Cosmetic assessments

| | |
|---|---|
| **STUDY DESIGN** | Phase III, multi-centre, randomised |
| **STUDY POPULATION** | 266 patients |
| **INCLUSION CRITERIA** | 1. Diagnosis of colorectal cancer<br>2. Suitable for elective resection following planned admission<br>3. ≥ 18 years of age<br>4. Written informed consent given |
| **EXCLUSION CRITERIA** | 1. Acute intestinal obstruction<br>2. Unplanned admission to hospital<br>3. Unsuitability for epidural insertion – determined pre-randomisation<br>4. Pregnant<br>5. Unsuitable for laparoscopic resection as conversion to open surgery is likely |

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