

MRC CLASICC TRIAL

Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer



Protocol

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Yorkshire Clinical Trials and Research Unit (YCTRU), Leeds
Department of Surgery, St James's University Hospital, Leeds
Department of Pathology, University of Leeds
Health Policy Unit, London
Centre for Research and Implementation of Clinical Practice, London

ADDRESSES AND TELEPHONE NUMBERS

Surgery:

Professor P J Guillou
Professor of Surgery, Academic Unit of Surgery
Level 8, Clinical Sciences Building
St James's University Hospital
Beckett Street, Leeds LS9 7TF
Tel: 0113 243 3144 ext: 5281

Pathology:

Dr P Quirke
Algernon Firth Institute, University of Leeds
Leeds LS2 9JT
Tel: 0113 233 3412
Fax: 0113 292 2834
Email: philq@pathology.leeds.ac.uk

Health Economics:

Professor N Bosanquet
Department of Primary Health, ICSM
Charing Cross Campus, Reynolds Building
St Dunstons Road, London W6 8RP
Tel: 020 7594 3358
Fax: 020 7594 0859

Dr P Franks
Centre for Research, Wolfson School of Health
Sciences, Thames Valley University
32-38 Uxbridge Road, London W5 2BS
Tel: 020 8280 5020
Fax: 020 8280 5285

Statistics:

Mrs J M Brown, Chief Medical Statistician
NYCTRU, 17 Springfield Mount, Leeds LS2 9NG
Tel: 0113 233 1499
Fax: 0113 233 1471
Email: medjmb@leeds.ac.uk

Trial Administration:

Dr Sue Bell, Senior Trial Co-ordinator
Miss Joanne Walker, Trial Co-ordinator
NYCTRU, 17 Springfield Mount, Leeds LS2 9NG
Tel: 0113 233 1492 / 1493
Fax: 0113 233 1471
Email: medseb@leeds.ac.uk
medjwa@leeds.ac.uk

Research Fellow:

Mr Adrian Smith
Academic Unit of Surgery
Level 8, Clinical Sciences Building
St James's University Hospital
Beckett Street, Leeds LS9 7TF
Tel: 0113 206 5282

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1. BACKGROUND TO THE STUDY

Colorectal cancer is the second most common malignancy in the western world with over 27,500 new cases per year in the United Kingdom. Adequate surgical resection is the only curative treatment, with overall survival rates of just under 50% at 5 years. Despite the hidden surgeon-related variability concealed within this overall figure (Phillips 1984b, McArdle 1990, MacFarlane 1992, Jatzko 1993), all are agreed that surgical technique is critical both in respect of cure and local recurrence. Accordingly, current conventional open surgery must be regarded as the 'gold standard' against which any modification of the technique must ultimately be judged.

The innovative application of laparoscopic procedures has reinvigorated general abdominal surgery in recent years. It is only eight years since Mouret performed the first laparoscopic cholecystectomy and since that time thousands of such procedures have been performed throughout the world and audit data alone have been utilised to support its introduction into routine clinical practice without the benefit of a randomised clinical trial. Indeed it has been argued that such a trial would now be unethical (Neugebauer 1991). The introduction of this procedure as the accepted standard operation for gallstones has occurred in the face of an acknowledged higher bile duct injury rate, at least in the first few years of its introduction, this being justified on the basis that these complications occurred during the surgeon's 'learning curve' for the procedure. On this basis, other procedures such as laparoscopic appendicectomy and inguinal hernia repair are also being rapidly incorporated into routine clinical practice before the results of large-scale clinical trials are available (MacIntyre 1992, Attwood 1992).

Inevitably surgeons with an interest in colorectal disease have also begun to explore the boundaries of this technology in their speciality with the hope that the perceived benefits of laparoscopic surgery in other arenas, namely less pain, earlier mobilisation, shorter hospital stay, earlier return to work and improved long-term cosmetic results, would also apply to laparoscopic colorectal surgery. The techniques of laparoscopic colorectal surgery have now been well described (Elftman 1994, Sackier 1992, Phillips 1992) and laparoscopic procedures designed to treat benign conditions of the colon and rectum are already popular amongst enthusiastic laparoscopic colorectal surgeons (Phillips 1992, Nezhat 1992, Miller 1992, Wexner 1992, Monson 1992). These operations are advocated by experienced colorectal surgeons who have acquired laparoscopic skills and such procedures may be evaluated through clinical audit without recourse to randomised clinical trials as has been the case with laparoscopic cholecystectomy. Such an approach is unacceptable in the case of malignant colorectal disease around which there is considerable debate (O'Rourke and Heald 1993). Preliminary evidence supports the protagonists' view that laparoscopic resection avoids prolonged ileus, significant post-operative pain and major morbidity secondary to large abdominal wounds (Monson 1992, Phillips 1992), but there is little or no evidence to support claims that the quantity or quality of life is improved for patients with or without co-existent metastases (Franklin 1993). These procedures have also been justified on the grounds that the extent of bowel and mesenteric resection which can be achieved laparoscopically is equivalent to those which are obtained with conventional open surgery (Lewis 1993). These claims are an attempt to allay fears that the laparoscopic approach results in less radical resection margins and would be associated with a higher incidence of loco-regional recurrence than is the case with conventional open surgery (Phillips 1992, Guillou 1993, Franklin 1993, Van Ye 1994). In reality, without prospective studies of the equally important resection margins (Quirke 1986) and actual recurrence rates it is difficult to be reassured that laparoscopic dissection does not compromise the current standards of surgical resection of a condition for which the only hope of cure lies with adequate surgical resection.

Having said all this, there is no evidence that the prognosis for those patients who have their colorectal cancers resected via the laparoscopic or laparoscopic-assisted technique is any worse than that of patients undergoing conventional open surgery except possibly in one regard, namely, the development of port-site recurrence. Port-site recurrences have been reported following laparoscopic removal of gallbladders subsequently found to contain occult primary adenocarcinomas (Clair 1993). Although tumour recurrence in the wound following conventional open colorectal resections for carcinoma is uncommon, there have been some misgivings in the surgical literature about port-site recurrences following laparoscopic or laparoscopic-assisted colorectal resections for cancer (Cirocco 1994, Johnson and Fligelstone 1993). However, in most instances review of moderate to large numbers of laparoscopic resections of colorectal cancers have come to the conclusion that the few port-site recurrences which have been reported occurred in patients with loco-regionally advanced disease or diffuse peritoneal carcinomatosis (Ramos 1994, Guillou 1993). Clearly this is an issue which can only be resolved by means of a prospective study.

The health care economics of laparoscopic surgery have been a cause of considerable concern throughout the world particularly in the western world where health care costs in general have been spiralling upwards. Whilst it is a relatively straightforward matter to determine the sum of the costs of performing a particular laparoscopic procedure and comparing these with those costs incurred when the procedure is performed conventionally via a laparotomy (Musser 1994), there are other components of cost-benefit and cost-effectiveness which require proper evaluation. This requires that measurements of quality of life be incorporated into the evaluation and in no clinical arena is this more important than in the evaluation of a surgical procedure applied to patients suffering from malignant disease, such as colorectal cancer, for whom surgical clearance is curative when conducted appropriately. Thus an important factor to be included in the equation is not only quality but duration of life without symptoms. Again this can only be satisfactorily investigated within the context of a randomised clinical trial.

The final issue with regard to the assessment of laparoscopic surgery for colorectal cancer is the rapidity with which the evaluation of an emerging technology can be conducted. It is self-evident that the answer to the question of the oncological safety of this approach is required as soon as possible, yet, to perform a trial in which the conventional endpoint for disease-free survival is the sole criterion of effectiveness would take at least 10 years to complete. Accordingly, in the design of the present trial, an additional approach has been adopted based on what we know of the local recurrence rates in patients with rectal cancer who have histologically positive circumferential resection margins (Quirke 1986, Adams 1994). In such patients the local recurrence rate is 70%-87% within two years, and so the use of this histological endpoint may serve as an 'early warning' indicator if the resection margins of one or other of the procedures proved to be more frequently positive than the other. Of course, some patients with histologically negative resection margins will also develop local recurrence (9%) and, under such circumstances, the conventional endpoint of disease-free interval will be employed.

In summary therefore, there are around the world pockets of enthusiasm for the use of laparoscopic or laparoscopic-assisted colorectal resection (Dean 1994, Peters 1993, Tate 1993) which, as far as resecting colorectal cancer is concerned, have been tempered by public acknowledgement that this requires evaluation by randomised clinical trial (Guillou 1994). The present protocol details such a trial whose aim is to provide, by the use of appropriate endpoints, as rapidly as possible, an evaluation of the role of laparoscopic or laparoscopic-assisted resection in the management of patients suffering from colorectal cancer.

Rationale for the design of this trial

The design of this trial has been led by a number of considerations:

- i. the request from the MRC's Health Technology Assessment Group of HSRB for clinical trials to be designed pragmatically and for multi-centre trials to be conducted amongst a relatively small number of centres;
- ii. the need to obtain answers relatively quickly to a technology-led modification of surgical practice which may have a major impact on survival from colorectal cancer and which may also have important health care economic considerations;
- iii. the acknowledgment that a similar trial sponsored by the US National Institute of Health (NIH) is already recruiting patients. We have deliberately set out to incorporate features which will permit direct comparisons to be made with the US data, particularly in relation to the data on recurrence and health care economics. The data from this trial could therefore be pooled with the US data. However, this protocol also contains features which are not included in the US trial, in particular the detailed pathology data. There is also a similar North European trial at the preliminary protocol stage. This trial could also supply data for a future meta-analysis.

2. AIMS AND OBJECTIVES

A randomised controlled trial of minimally invasive surgery for colorectal cancer is required in order to answer the following questions:

- Are longitudinal and circumferential resection margins and lymphatic clearances obtained during laparoscopic surgery different from those obtained with conventional open surgery?
- Is the pattern of loco-regional or distant metastatic spread any different after laparoscopic surgery from that seen after conventional open surgery?
- Does laparoscopic colorectal resection possess an intrinsically different morbidity and mortality rate compared to conventional open surgery, particularly in terms of the technical or thromboembolic complications which may develop as a consequence of prolonged pneumoperitoneum?
- Is the disease-free or overall survival different for the two operative procedures?
- In those patients in whom laparoscopic surgery fails (approximately 8-10% of cases: Guilleu 1993), which investigatory modalities are appropriate for providing pre-operative indications that a patient is an inappropriate candidate for laparoscopic dissection?
- Are there differences in perceived health, ie, quality of life, between the two operative procedures, in particular for those patients with advanced disease?

- What are the relative costs of the standard method of open resection and the laparoscopic method?
- Is there a difference in terms of cost-utility between the two treatment groups?

3. DESIGN

This trial is a randomised, multi-centre trial of laparoscopic versus conventional open resection for colorectal cancer. The design involves unequal allocation of patients to the two procedures in a 2:1 allocation of laparoscopic to open resection. The trial is stratified by surgeon, proposed site of operation, presence of liver metastases, if known, and decision regarding pre-operative radiotherapy administration.

4. PROTOCOL TREATMENT

4.1 Pre-operative Care

Bowel preparation and prophylactic antibiotic regimen will be standardised in each centre. All surgeons should use stockings and low dose subcutaneous heparin for deep vein thrombosis prophylaxis.

4.2 Intra-operative Care

Anaesthetic care will be standardised by individual surgeons for all of their patients throughout the trial, where possible. The manner of anastomosis will be based on surgeon's preference. Heparin should be included in the peritoneal lavage in all patients.

4.3 Surgical Procedure

Surgery should be carried out according to current practice. Conventional and laparoscopic surgery should be undertaken according to the same protocol by the same surgeon, the only difference being in the manner of exposure.

Poorly differentiated, very low rectal lesions (<5 cm from anal verge) should be treated by abdomino-perineal excision. For each abdomino-perineal resection, the surgeon should justify why this procedure was performed instead of a sphincter-preserving operation since recent publications have suggested an intrinsic selection bias in patients receiving abdomino-perineal resection (Franklin 1993).

4.4 Pathology

Detailed pathological examination of resected specimens will be undertaken by a nominated local pathologist, according to an established technique which focuses on the extent of circumferential resection margin (Quirke and Dixon 1988). Pathologists will receive the surgical specimen either in formalin or fresh. The methodology for review is an update of the UKCCCR Colorectal Cancer Subcommittee Handbook on Colorectal Cancer (UKCCCR 1989) which is currently used in the AXIS trial. Details of the method can be found in Appendix 1. Data to be provided by the local pathologist are detailed in Section 8. Central review of the histology will be performed; a second set of haematoxylin and eosin sections and two 2cm x 2cm colour slides should be sent to the YCTRU for this central review.

4.5 Follow-up

Follow-up should be at one and three months following surgery, then at three-monthly intervals for the first year, four-monthly in the second year and six-monthly subsequently.

5. ELIGIBILITY

Inclusion criteria

Patients must

- have a clinical diagnosis of colorectal cancer. This clinical diagnosis should be based on colonoscopy or barium enema (according to each centre's current practice) undertaken within 30 days of planned date of operation*

(* This diagnosis should be histologically confirmed following surgery.)

- be suitable for elective surgical resection by right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection or abdomino-perineal resection†

(† Lesions of the lower/middle third of the rectum suitable for low anterior resection can be included. Surgeons should state at the outset of the trial whether they are willing to randomise such patients.)

- be aged ≥ 18 years
- give written informed consent.

Exclusion criteria

Patients should not

- have adenocarcinoma of the transverse colon
- have any contraindication to pneumoperitoneum such as severe cardio-respiratory disease
- have acute intestinal obstruction
- have had malignancy within previous five years (except basal cell carcinoma, *in situ* carcinoma of cervix or prostate cancer)
- have synchronous multiple adenocarcinomas
- if female, be pregnant
- have associated gastrointestinal disease that requires surgical intervention, eg. Crohn's, chronic ulcerative disease, familial polyposis.

6. ADJUVANT THERAPY

Adjuvant chemotherapy or radiotherapy may be administered to patients. This may be given within the context of a randomised trial such as QUASAR or AXIS.

6.1 Pre-operative Radiotherapy

If pre-operative radiotherapy is to be given, it must be given or planned to be given before randomisation into this trial.

If pre-operative radiotherapy is to be randomised within the AXIS trial, the AXIS randomisation should be undertaken prior to randomisation into this trial. In this trial randomisation will be stratified by whether pre-operative radiotherapy has been given or not.

6.2 Post-operative Radiotherapy and Chemotherapy

Differential staging of disease or rates of recovery from surgery between the two types of operation may lead to different rates of administration of adjuvant therapy in the two arms. If this happens, it may not be possible to evaluate the effect of surgery separately from that of adjuvant therapy. It is therefore important that the adjuvant therapy is not decided on the basis of type of operation. For this reason surgeons will be asked at the outset to state their protocol for use of adjuvant therapy in the trial. Surgeons will be asked to state in particular for each stage of colon and rectal cancer whether they would never, occasionally, usually or always give adjuvant therapy. The use of adjuvant chemotherapy or radiotherapy will be closely monitored for the surgeon against the stated protocol, and surgeons will be asked to update their protocol or give reasons for deviations from it.

It will be possible to enter patients into both the CLASICC Trial and to either QUASAR or AXIS. The following sections indicate the timing of randomisations into these trials.

6.2.1 Randomisation into the CLASICC Trial and QUASAR - for patients with colorectal cancer

Randomisation into QUASAR should take place after surgery, ie. after randomisation into the CLASICC Trial.

6.2.2 Randomisation into the CLASICC Trial and AXIS - for patients with colonic cancer

In AXIS, only one randomisation is available for patients with colonic cancer: intraportal 5-FU vs no intraportal 5-FU. Since intraportal 5-FU is difficult with laparoscopic surgery, patients with colonic cancer **cannot** be entered into both the CLASICC and AXIS trials.

6.2.3 Randomisation into the CLASICC Trial and AXIS - for patients with rectal cancer

In AXIS, patients with rectal cancer can be randomised with respect to 5-FU infusion and with respect to pelvic radiotherapy. Radiotherapy may be pre- or post-operative but the intended treatment must be stated at the time of randomisation into AXIS.

Patients who are to be randomised for pre-operative radiotherapy without 5-FU should be randomised into AXIS before surgery, ie. before randomisation into the CLASICC Trial.

Patients who are to be randomised for post-operative radiotherapy only (ie. not for intraportal 5-FU) should be randomised into AXIS after surgery, ie. after randomisation into the CLASICC Trial.

Any patient considered for intraportal 5-FU **cannot** be randomised into both the CLASICC and AXIS trials.

6.2.4 Summary of timing of randomisation into AXIS and QUASAR with respect to the CLASICC Trial

Before CLASICC Trial

AXIS: rectal cancer - randomisation for pre-operative radiotherapy only.

After CLASICC Trial

1. AXIS: rectal cancer - randomisation for post-operative radiotherapy only.
2. QUASAR: colon or rectal cancer - all randomisations.

The entry of patients into these trials will be strictly monitored against the adjuvant therapy guidelines given by the individual surgeons.

If chemotherapy is to be given in addition to radiotherapy, it is recommended that radiotherapy be given pre-operatively to avoid disrupting chemotherapy and because evidence suggests that pre-operative radiotherapy may be at least as effective as post- at preventing recurrence.

7. REGISTRATION / RANDOMISATION

Patients will be entered into the trial by a telephone call to the Yorkshire Clinical Trials and Research Unit (YCTRU) (0113 233 4930 Monday-Friday 9 am-5 pm except public/Bank Holidays). Informed written consent for entry into the study should be obtained prior to randomisation. The following information will be required at randomisation:

- name of surgeon
- basic patient details: date of birth, name and address
- site of proposed operation
- whether a liver ultrasound has been carried out within 30 days of planned date of operation to determine presence of liver metastases
- WHO performance status

- confirmation of eligibility and written informed consent (see Appendix 2 for Eligibility Checklist)
- pre-operative radiotherapy decision
- other clinical trials into which patient will be entered
- date of planned operation
- proposed operative procedure
- confirmation that the patient has agreed to take part in the health economics and quality of life studies.

Once eligibility has been confirmed and the necessary details obtained, the patient will be randomised to laparoscopic or conventional open dissection, and allocated a trial number. The randomisation will be an unbalanced (2:1 laparoscopic to conventional) stratified randomisation. Stratifying factors will be surgeon, proposed site of operation, presence of liver metastases and decision about radiotherapy treatment. The strata will be defined as follows:

- Surgeon
- Proposed site of operation
 - a. left and sigmoid colon
 - b. right colon
 - c. rectum - anterior resection
 - d. rectum - abdominoperineal resection
- Presence of liver metastases as investigated by liver ultrasound within 30 days of planned date of operation
 - a. present
 - b. absent
 - c. not investigated
- Radiotherapy decision
 - a. pre-operative radiotherapy given/to be given
 - b. pre-operative radiotherapy not given/not to be given.

Surgeons require notice of randomised procedure in order to plan theatre lists. The patient must be randomised as late as possible and at most 14 days before surgery; however, this can be extended up to 28 days depending on the local situation.

8. DATA COLLECTION

All data including the health economics and quality of life data will be collected, monitored and computerised centrally by the YCTRU. All patients who are approached to enter the trial should be logged including those who refuse randomisation. Brief details of the reasons why patients are not randomised should be given, including where possible reasons for non-consent.

Data collection has been reduced to the minimum with the majority of the data collection being completed by the Research Fellow from the patient's case notes and the operating theatre records.

The surgeon will need to complete an eligibility checklist, before telephoning the YCTRU to enter the patient into the trial, and two forms at operation. All the other data required will be completed by the Research Fellow except for the annual follow-up data and the questionnaires completed by the patients themselves.

8.1 Main study

Pre-randomisation

The following information will be collected for the period prior to randomisation. This will be extracted from the patient's notes by the Research Fellow.

- patient details: date of birth, name, sex, NHS number, and GP's name and address
- surgeon's name
- height and weight (will be used to calculate body mass index)
- haematology: full blood count, platelets, urea, electrolytes, liver function tests
- diagnosis, date of diagnosis and diagnostic method
- tumour site
- number of blood transfusions in the seven days before operation (and whether they were autologous or allogenic)
- date of admission
- details of pre-operative radiotherapy, if applicable.

At randomisation

Prior to randomisation the surgeon will complete an eligibility checklist (see Appendix 2) which will be sent to the YCTRU as soon as possible after randomisation. At randomisation the surgeon will be asked to give the following information over the telephone:

- patient's name and date of birth
- surgeon's name
- eligibility criteria fulfilled (according to the completed checklist) and written informed consent obtained from the patient
- site of proposed operation
- whether a liver ultrasound has been carried out 30 days before planned date of operation to determine presence of liver metastases
- WHO performance status
- radiotherapy decision:
 - a. pre-operative radiotherapy given/to be given
 - b. pre-operative radiotherapy not given/not to be given
- other clinical trials patients to be entered into
- date operation planned
- operative procedure to be carried out.

At surgery

The following information will be provided by the surgeon:

- name of surgeon
- previous abdominal incisions - number and position (the latter will be indicated by the surgeon on a diagram of the abdomen and coded by the YCTRU by dividing it up into sections, using a template, each section being assigned a code number)
- position of incision for laparoscopic and open procedures (to be collected diagrammatically)
- date of operation
- operative procedure performed: ie. right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection, sub-total colectomy, pan-proctocolectomy, abdomino-perineal resection
- procedure accomplished: ie. laparoscopic mobilisation, intracorporeal vessel division, extracorporeal vessel division, intracorporeal bowel division, extracorporeal bowel division, intracorporeal anastomosis
- curative, palliative or unresectable procedure
- presence of liver or peritoneal metastases
- where appropriate, reasons why abdomino-perineal excision was performed
- use of a bag to recover specimen when being removed
- whether a colonoscopy was carried out during operations
- ASA grade
- intra-operative complications
- site of stoma, if applicable
- type of anastomosis
- if rectal carcinoma, whether a TME was performed.

The following data will be recorded by the pathologist:

- patient details
- gross description: site of tumour and length of specimen
distance of tumour from distal and proximal margins
position of rectal tumours: above, at or below peritoneal reflection
distance of tumour from nearest surgical high tie on vascular pedicle
- histology: type and differentiation
- extent of local invasion: maximum distance of spread of tumour from muscularis propria
- margins: involvement of circumferential and longitudinal excision margins
histological measurement of distance from tumour to circumferential margin where appropriate
- peritoneal spread: presence of peritoneal seedlings or peritoneal involvement
- metastatic spread: number of lymph nodes examined
number of positive lymph nodes
involvement of (C2 or pN3) apical node
histological evidence of distant metastases
- synchronous adenoma(s)
- synchronous carcinoma(s)
- other conditions: ulcerative colitis
familial adenomatous polyposis
Crohn's disease
- pathological staging: Dukes'
TNM
resection completed at all margins

The pathologist will also send to the YCTRU a set of haematoxylin and eosin sections and three colour slides of the resected specimen, including the front and back of the specimen with the area of the tumour unopened and a picture of the sliced tumour. These will be forwarded to the YCTRU for central review.

Tumours are classified according to the R classification:

- R0 Complete clinicopathological curative resection.
- R1 Residual microscopic disease. This would include margin involvement by microscopic tumour.
- R2 Residual macroscopic disease.

Central pathology review

The YCTRU will ensure that the pathology data, slides and sections returned from each centre are anonymised, so that the pathologist undertaking the central review remains blind to surgeon, centre, and type of operation.

All the pathology data and other material will be reviewed regularly throughout the trial.

The data listed below will be provided by the pathologist undertaking the central review:

- presence of adenocarcinoma, grade, margin, inflammatory reaction
- distance of the tumour from:
 - the muscularis propria
 - the circumferential margin
 - the longitudinal margins
 - high tie
- area of tumour, fat and normal colorectal tissue of the slice with smallest distance to circumferential margin
- peritoneal involvement
- Dukes' stage
- TNM classification
- description of :
 - shape and smoothness of resected specimen
 - amount of fat around the specimen.

On central review there will be a subjective assessment of the quality of rectal surgery.

- Poor Muscularis propria can be seen in any area of the posterior mesorectum.
- Moderate No muscularis propria visible but irregular surface of back of mesorectum and mild to moderate amount of fat.
- Good Bulky mesorectum or smooth surface covered by mesorectal fascia.

8.2 Socio-economic Study

8.2.1 Quality of Life Assessment

Quality of life will be assessed by patients' self-reported symptoms and patients' self-reported utilities. Patients who are willing and able to give informed consent to participate in the quality of life study and who are able to read and complete the questionnaire are eligible for entry into this study.

Many commonly used tools for the assessment of quality of life are generic, being designed for use over a wide range of chronic diseases. Examples of these are the Nottingham Health Profile and MOS short form health survey. However, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Study Group has devised a disease-specific tool for assessing patients suffering from cancer, which can be adapted for different disease sites (Sprangers 1993, Aaronson 1991). This tool (the EORTC QLQ-C30) has the advantages that it is a self-administered multi-dimensional assessment including questions on fatigue, nausea and vomiting, whilst providing scores for emotional and social functioning and overall quality of life assessment. The tool was developed in several countries and has good validity and reliability across languages and cultures. The EORTC QLQ-C30 will be used in this trial and also in the QUASAR trial. The EORTC QLQ-C30 does not measure gastrointestinal-specific symptoms, so these will be assessed by a colorectal module (QLQ-CR38) which is currently being developed by the EORTC Quality of Life Study Group (Sprangers, in preparation).

Self-reported utility will be measured by EuroQol. The EuroQol instrument is a standardised non-disease-specific instrument which describes and values health-related quality of life and provides a single index value for a number of different health states (EuroQol group, 1990). EuroQol is intended to complement other quality of life measures and can be administered as a postal questionnaire.

8.2.2 Health Economics Data

There are no standard procedures for collecting health economics data, since there is such a broad spectrum of potential costs involved. In this trial all patients entered into the socio-economic study will be required to complete questionnaires on the use of health resources. The health resources questionnaire will provide information about the patient's use of the health service before operation or since the previous follow-up. Data to be collected include GP surgery visits, GP home visits, in-patient stays, out-patient visits, occupational therapy usage, hospital transport and the use of social services, for example home help, residential home usage, carer usage, meals on wheels, community transport, physiotherapy usage, visits by district nurse. Only a small subset of patients will have an in-depth assessment of costs related to the operative procedure (see Section 10, Sample Size). Other data items, such as the length of time spent in the operating theatre and details on adjuvant therapies, will be recorded for all patients in the main dataset.

Operative Procedure

The following data will be collected for a small subset of patients (Section 10):

- anaesthetic details including use of pre-medication
- operative medication
- length of time in recovery room and time to return to ward
- details including grades of surgical team and ancillary staff
- disposables used during operation: swabs, masks, sutures, blood units
- sterile equipment: gowns and sheets
- non-sterile gowns and sheets.

8.2.3 Key worker

Each centre will be asked to delegate a key worker, where possible a research nurse, to be responsible for the health economics and quality of life pre-operative assessment at a local level. This will involve explaining the questionnaires and the required follow-up to the patients, and then checking patients' current status before the YCTRU sends out subsequent follow-up questionnaires. The YCTRU will contact this local key worker at regular intervals. A workshop for key workers will be held prior to the launch of the trial to explain the plan and purpose of the health economics and quality of life studies and to standardise procedures throughout each centre.

8.2.4 Timing of Data Collection

ii. Pre-operative

Patients will be interviewed by the key worker to assess basic demography details and to collect details of the patients' use of health resources during the past three months.

The key worker will also explain to the patient how to complete the EORTC QLQ-C30 and QLQ-CR38, and the EuroQol questionnaires. Patients will be required to complete these questionnaires themselves.

Therefore, data to be collected pre-operatively are as follows:

- basic demography details
- use of health service resources over past three months
- EORTC QLQ-C30
- EORTC QLQ-CR38
- EuroQol.

ii. Two weeks post-operative

Data collected two weeks post-operatively will provide information in the immediate post-operative period for changes in perceived health and limited data on the patient's post-operative progress. In addition it will detail information on the patient's return to work, if applicable. The questionnaires will be administered by post from the YCTRU or by the key worker if the patient is still in hospital. For patients who do not survive to this date, the data will be collected wherever possible from the hospital and GP records.

Therefore, data to be collected are as follows:

- date of return to work, if applicable
- use of health service resources since surgery
- EORTC QLQ-C30
- EORTC QLQ-CR38
- EuroQol.

iii. Three months post-operative

Data collected three months post-operatively will provide information on further use of health resources, changes in perceived health and information on the patient's return to work. The questionnaires will be administered by post by the YCTRU. The YCTRU will endeavour to check the patient's current status with each centre before sending out questionnaires, as up-to-date follow-up information should be available from the three-month clinic visit. Data to be collected are as for the two-week post-operative assessment.

iv. Six months post-operative

Data collected six months post-operatively are again aiming to observe changes in health status whilst attempting to determine the level of support required from acute and community services. The questionnaires will be administered by post by the YCTRU. The YCTRU will check the patient's current status with each centre before contacting patients. Up-to-date follow-up information should be available from the six-month clinic visit. Data to be collected are as for the two-week post-operative assessment.

v. 18 months post-operative

Data collected 18 months post-operatively will provide similar information on health status, use of resources and level of support as for the previous assessments. The questionnaires will again be administered by post. At this point, follow-up information should be available from the 16-month clinic visit. Data to be collected are as for the two-week post-operative assessment.

vi. 36 months post-operative

Data collected 36 months post-operatively will provide similar information on health status, use of resources and level of support as for the previous assessments. The questionnaires will again be administered by post. At this point, three-year follow-up information should be available. Data to be collected are as for the two-week post-operative assessment.

When questionnaires are administered by post, they will be sent directly to the patient with a stamped, addressed envelope for their return to the YCTRU. Patients will be sent a follow-up letter if they do not return questionnaires within four weeks. A letter of thanks will be sent to each patient returning the questionnaire. It is important that the YCTRU is notified of the dates of death as soon as possible to avoid sending letters to deceased patients.

9. ENDPOINTS

Primary endpoints are:

- circumferential, longitudinal and high tie mesenteric resection margins as recorded on central pathology review
- 30-day operative mortality
- local recurrence rate at three years
- disease-free survival at three years
- overall survival at three years.

Secondary endpoints are:

- disease-free and overall survival at five years
- port-site and wound site recurrences
- complication rates (operative morbidity)
- quality of life and cost effectiveness
- blood transfusion requirements
- loco-regional, anastomotic and distant metastases.

10. SAMPLE SIZE

Practical constraints due to the number of surgeons experienced in this laparoscopic technique, the urgency of data collection in a trial for laparoscopic surgery and the possibility of combining data from this trial with that of the US trial (see below) have led to a decision that 1,000 patients is the maximum achievable sample size in a reasonable length of time. There are 16 centres and 18 surgeons participating in the trial (see Appendix 5 for list of participants). It is anticipated that the recruitment target can be achieved in three years and that once the trial is ongoing more surgeons will be eligible to participate in the trial. Every effort will be made throughout the trial to encourage more surgeons and more centres to take part.

It will take a further three years for preliminary recurrence and survival data to be available and a further five years until final results are available.

The sample size of 1,000 colorectal cancer patients will not have enough power to be able to detect whether the two surgical procedures are equivalent in terms of the main endpoints. There will also be limited power to examine the effects of the two procedures in subgroups of patients. In particular, with the exception of the positive resection margins, this trial will not have the power to detect effects for colonic and rectal cancer patients separately. Strong inconsistencies in subgroups, such as those with metastases or curative versus palliative resection will, however, be reported.

Consequently, it is proposed that data from this trial should be pooled with that from the US trial. The US trial is already recruiting patients and is being run under the auspices of the US National Institute of Health. The trial is examining the efficacy of laparoscopic-assisted colectomy versus open colectomy for colonic cancer. The trial is aiming to recruit 1,200 colonic cancer patients and the primary endpoint is three-year recurrence-free survival. A second major analysis of overall survival will be performed when all the patients have been followed for seven years. The survival endpoints for this trial have been chosen therefore to reflect those in the US trial. Pooling the data from the two trials will increase the power to address the questions of equivalence of all cause and disease-free survival for colonic cancer patients.

To allow for the approximate 10% conversion rate from laparoscopic surgery to open surgery, and to enable as much information as possible to be collected on laparoscopic surgery, it is proposed that the randomisation for this trial will be unbalanced. The imbalance chosen in this trial is 2:1 which results in a relatively small reduction in power compared to a trial with balanced randomisation.

As there is insufficient power for this trial to examine equivalence in isolation, it is proposed to examine the absolute difference between the two surgical techniques in relation to the main outcomes. Confidence intervals for the likely differences for each of the main outcomes are set out below.

10.1 Positive Resection Margins

10.1.1 Positive circumferential resection margins

With conventional open surgery, 25% of patients with rectal cancer will be expected to have positive circumferential resection margins (Adam 1994). In 1,000 colorectal cancer patients approximately 380 will be rectal cancer patients (Cancer Statistics Registrations, OPCS Series MB1 No. 22, 1989). The table below shows the likely width of the 95% confidence interval for a 2:1 design for various absolute differences in the proportion of positive circumferential resection margins for the number of patients to be recruited.

Total no. of Patients	Proportion of positive circumferential resection margins		Difference in proportion of positive margins	95% CI for difference
	Open Surgery	Laparoscopic Surgery		
380	25%	27%	2%	(-7%, 11%)
380	25%	30%	5%	(-4%, 14%)
380	25%	35%	10%	(1%, 20%)
380	25%	40%	15%	(5%, 25%)

10.1.2 Positive longitudinal resection margins

With conventional open surgery, approximately 5% of patients with colorectal cancer will be expected to have positive longitudinal resection margins (Quirke 1995). In 1,000 colorectal cancer patients approximately 620 will be colonic cancer patients (Cancer Statistics Registrations, OPCS Series MB1 No. 22, 1989). The table below shows the likely width of the 95% confidence interval for a 2:1 design for various absolute differences in the proportion of positive longitudinal resection margins for the number of patients to be recruited.

Total no. of Patients	Proportion of positive longitudinal resection margins		Difference in proportion of positive margins	95% CI for difference
	Open Surgery	Laparoscopic Surgery		
620	5%	7%	2%	(-2%, 6%)
620	5%	10%	5%	(1%, 9%)
620	5%	15%	10%	(5%, 15%)
620	5%	20%	15%	(10%, 20%)

10.1.3 Positive high tie mesenteric resection margins (proportion of Dukes' C2 tumours)

With conventional open surgery, approximately 9% of patients with colorectal cancer will be classified as Dukes' C2 - based on number of lymph nodes involved or apical node involvement (Phillips 1984a). The table below shows the likely width of the 95% confidence interval for a 2:1 design for various absolute differences in the proportion of positive high tie mesenteric resection margins for the number of patients to be recruited.

Total no. of Patients	Proportion of positive high tie mesenteric resection margins		Difference in proportion of positive margins	95% CI for difference
	Open Surgery	Laparoscopic Surgery		
1000	9%	11%	2%	(-2%, 6%)
1000	9%	14%	5%	(1%, 9%)
1000	9%	19%	10%	(6%, 14%)
1000	9%	24%	15%	(11%, 19%)

10.2 Operative Mortality

The incidence of 30-day operative mortality from conventional surgery for colorectal cancer ranges from 4% (Goodman and Irvin 1993) to 14% (McArdle 1990). The table below shows the likely width of the 95% confidence interval for a 2:1 design for various absolute differences in the incidence of operative mortality for the number of patients to be recruited.

Total no. of Patients	Incidence of operative mortality		Difference in incidence of operative mortality	95% CI for difference
	Open Surgery	Laparoscopic Surgery		
1000	4%	6%	2%	(-1%, 5%)
1000	4%	9%	5%	(2%, 8%)
1000	4%	14%	10%	(7%, 13%)
1000	4%	19%	15%	(11%, 19%)
1000	14%	16%	2%	(-3%, 7%)
1000	14%	19%	5%	(0%, 10%)
1000	14%	24%	10%	(5%, 15%)
1000	14%	29%	15%	(10%, 20%)

10.3 Three-year Local Recurrence Rates

The overall three-year local recurrence rate for colorectal cancer is 12% (Phillips 1984b). The table below shows the likely width of the 95% confidence interval for a 2:1 design for various absolute differences in the three-year local recurrence rates for the number of patients to be recruited.

Total no. of Patients	Three-year Local Recurrence Rate		Difference in Recurrence Rates	95% CI for difference
	Open Surgery	Laparoscopic Surgery		
1000	12%	14%	2%	(-2%, 6%)
1000	12%	17%	5%	(0%, 9%)
1000	12%	22%	10%	(5%, 15%)
1000	12%	27%	15%	(10%, 20%)

10.4 Three-year Survival

10.4.1 Three-year Disease-free Survival

The three-year colorectal cancer specific survival is approximately 60% (Murray 1995). The table below shows the likely width of the 95% confidence interval for a 2:1 design for various absolute differences in the three-year disease-free survival rates for the number of patients to be recruited.

Total no. of Patients	Three-year Disease-free Survival Rate		Difference in Survival Rates	95% CI for difference (in favour of open surgery)
	Open Surgery	Laparoscopic Surgery		
1000	60%	58%	2%	(-4%, 8%)
1000	60%	55%	5%	(-1%, 11%)
1000	60%	50%	10%	(4%, 16%)
1000	60%	45%	15%	(9%, 22%)

10.4.2 Three-year All Cause Survival

The three-year all cause survival is approximately 50% (Murray 1995). The table below shows the likely width of the 95% confidence interval for a 2:1 design for various absolute differences in the three-year all cause survival rates for the number of patients to be recruited.

Total no. of Patients	Three-year All Cause Survival Rate		Difference in Survival Rates	95% CI for difference (in favour of open surgery)
	Open Surgery	Laparoscopic Surgery		
1000	50%	48%	2%	(-5%, 9%)
1000	50%	45%	5%	(-2%, 12%)
1000	50%	40%	10%	(3%, 17%)
1000	50%	35%	15%	(9%, 21%)

Many of the post-operative rates associated with conventional surgery are tentative. Close attention will be paid therefore to monitoring these rates on the conventional arm with a view to increasing the target sample size if deemed essential by the Data Monitoring Committee. If an increase in the rate of accrual is required, then it is expected that by that time additional surgeons will be eligible to participate in the trial.

10.5 Quality of life data

500 patients will be entered into the quality of life assessment. This will provide over 80% power, if follow-up is reasonably complete, to detect differences of 10-15% in proportions of patients in quality of life categories between the two arms (type I error 1%). An overall type I error of 1% has been chosen because of the multiple comparisons which will be undertaken in the analysis.

In order to achieve this sample size, data will be collected on the first 500 patients randomised into the trial. Data will therefore be collected on approximately 340 laparoscopic patients and 170 conventional surgery patients.

10.6 Economic data

The operative procedure

It is anticipated that the detailed technical costs of the two techniques can be determined in a relatively small group of patients.

Although the surgery will be the same, it is likely that there will be minor differences in pre-operative and peri-operative assessment, surgical technique and post-operative protocols. It is proposed that detailed costs be determined in a random sample of ten patients undergoing each procedure from each centre. This will allow for a detailed cost to be derived from over one

hundred standard and one hundred laparoscopic procedures within the trial, and allow for any major differences in technique between the centres.

Use of health resources

The impact of the different surgical procedures on the patients' post-operative recovery will be performed on a sample of the total. The steering group acknowledges the importance of this trial to the MRC and wish to ensure that the data are collected in a standardised fashion. With this in mind, it is proposed that data collection on the economic analysis will be collected on the first 500 patients randomised into the trial. There are no standard methods of assessing sample size in cost analysis. Any sample size calculation will thus be speculative. It is proposed that the 500 patients selected for the quality of life assessment will enter the health economics study within the trial. This should provide information on the accuracy of costing methods for different sample sizes in any future studies.

11. ANALYSIS

All analyses will be carried out on an 'intention to treat' basis.

Thirty-day operative mortality, positive resection margin, local recurrence and complication rates will be compared between the two procedures using the Pearson Chi-squared Test. In addition to these analyses, the Mantel Haenszel Chi-squared Test will be used to adjust the analysis for covariates of interest. Covariates considered to be of interest include sex, age, Dukes' stage, the use of adjuvant therapy, presence of metastases at diagnosis, use of allogenic versus autologous blood transfusion, age and histologic differentiation. Multivariate analyses such as logistic regression may also be undertaken.

Disease-free and overall survival (time from randomisation to the endpoint) will be compared between the two procedures using the log-rank statistic. In addition Cox's Proportional Hazards Model will be used to adjust the analysis for covariates of interest (covariates detailed above).

The algorithms developed for use with the quality of life questionnaires will be used to summarise categories of interest. The two operative groups will be compared at each time point for differences between these categories. Data for the EORTC questionnaire will be compared between the two operative groups using a fixed effects model for repeated measures. Missing data will be handled by using either the Expectation Maximisation Algorithm (Dempster 1972) or the method suggested by Zwinderman (1992). For the economic analyses, the primary variable of interest will be the utility obtained from the EuroQol 0-100 scale. Mean treatment time and scores will be transformed to generate utilities according to the power function developed by Torrance (1987). The comparison of groups for cost utility using EuroQol will be performed using a repeated measures ANOVA.

Quality adjusted life years will be obtained using Q-TWIST analysis (Gelber 1986, Goldhirsch 1989), using utility weights calculated from the EuroQol scale in each treatment group. Four health states will be included in the Q-TWIST analysis: the peri-operative period, adjuvant therapy, TWIST and relapse, as in the US trial.

The duration of the peri-operative period will be defined as the first 30 post-operative days. The duration of adjuvant therapy will be measured from the date of first therapy until 30 days after the last dose of therapy. TWIST will be defined as the time from the end of the peri-operative period to recurrence or study end, whichever comes first, less the duration of adjuvant therapy. Relapse will include time from diagnosis of recurrence until death or end of study.

Utility assessment for the peri-operative period will be obtained from the patient's EuroQol measures at two weeks post-operatively. The utility for adjuvant chemotherapy will be the mean reported value among patients receiving chemotherapy at the time of the three-month post-operative quality of life assessment. The utility weight for TWIST will be the mean utility value obtained at 18 months post-operatively among patients remaining disease-free at that time. The utility for relapse will be arbitrarily set at 0.5, because by definition the patients' quality of life at the beginning of the period will be approximately 1 and will decline to 0 at the time of death. Sensitivity analyses will be carried out to ascertain the impact this arbitrary value has on the conclusions. The Q-TWIST calculations will be performed using software supplied by Gelber. The time horizons for the quality adjusted survival analysis will be the same as for survival three and five years after the last patient is enrolled.

Interim Analysis

Interim analyses of the primary endpoints will be undertaken at approximately yearly intervals and will be supplied, together with any other analyses the Committee may request, to the Data Monitoring Committee in strict confidence. In the light of the interim analyses, together with other evidence which may become available (for example from other trials), the Data Monitoring Committee will advise the trial co-ordinators on many issues including whether accrual to the trial should be stopped or continued.

12. QUALITY ASSURANCE

Quality control of the surgery will be monitored in various ways. It should be noted that participation in the trial will be limited to surgeons who have undertaken at least 20 laparoscopic and open colorectal operations. It is assumed, as in the US Trial, that maximal learning occurs between 12-20 laparoscopic cases. Any new surgeons entering the trial will sign a letter to confirm participation and the proposed number of patients they will enter into the trial.

In addition, as in the US Trial, surgeons will be asked to store unedited videos of all their laparoscopic operations performed on trial patients, so that they will be available for review if required.

The rate of conversion from laparoscopic to conventional surgery will be monitored. Previous results show on average 10% of procedures will be converted. Individual surgeons with a conversion rate of more than 20% will be drawn to the attention of the Data Monitoring Committee.

The rate of conversion from anterior resection to abdomino-perineal resection will be monitored to ensure that it does not differ between the types of operation.

Most importantly, the quality of the surgery will be monitored through the central review of the pathological data which is to be collected.

2cm x 2cm transparency photographs of the whole specimen, and the sliced tumour will also be reviewed (a centimetre scale should be included with each photograph).

Measurement of the following will be made:

- distance of the tumour from the muscularis propria
- distance of the tumour from the circumferential and longitudinal resection margin (photo and microscopy). These measurements will allow a comparison of the quality of surgery and the extent of the spread of tumour, as well as an indication of the accuracy of the local pathological measurements
- area of tumour, fat and normal residual colorectal tissue on the slice with the circumferential margin involvement or the greatest extent of spread slide
- distance of the tumour to the high tie.

The picture of the posterior aspect of the specimen will allow a record to be kept of the resected circumferential margin, enabling a subjective assessment of the volume of tissue removed to be made. This will allow early insight into whether there are major problems with laparoscopic rectal resection. Major problems with laparoscopic colon resection will be monitored by recording the number of specimens with less than 5 cm of fresh surgical margin between the line of proximal or distal resection and the primary tumour. This is also being utilised in the US Trial as an early indicator of major problems with laparoscopic colon resection. Estimates of the amount of tissue excised will provide a quantitative measure of quality, qualitative measures will include monitoring of the shape, smoothness and amount of fat around the specimen.

The pathologist undertaking the central review will be blind to surgeon and type of operation when undertaking the review. Any problems identified will be taken to the Data Monitoring Committee which will decide upon the appropriate action to be taken.

13. TRIAL ORGANISATION

13.1 Yorkshire Clinical Trials and Research Unit

The YCTRU will be the main co-ordinating centre and will be responsible for randomisation, all data collection and data management, monitoring and analysis of the main trial data. The YCTRU has considerable experience particularly in the cancer field; it is currently successfully co-ordinating the national MRC Myeloma VII trial which aims to recruit approximately 750 patients and involves collection of detailed immunological data and quality of life data. The Unit has the software and hardware to design project-specific databases which incorporate automatic data validation and data chasing. All data, including quality of life and health economics data, will be collected and validated by the YCTRU.

The YCTRU will be responsible for providing feedback to all trial participants, producing regular newsletters with up-to-date information on the trial, and organising meetings of collaborators which will be held to discuss any problems and other developments in the conduct of the study.

13.2 Centre for Research and Health Policy Unit

The Centre for Research and Implementation of Clinical Practice, London, and Health Policy Unit, London, will be responsible for the analysis of the health economics data.

13.3 Clinical Co-Ordination

Surgical Committee

Chair: Professor PJ Guillou

The Surgical Committee will consist of the Research Fellow and all surgeons participating in the trial. This Committee will agree the surgical guidelines at the beginning of the trial. It will meet regularly throughout the trial to receive feedback, particularly on recruitment rates and to discuss any problems which arise from the protocol.

Pathology Committee

Chair: Dr P Quirke

The Pathology Committee will consist of the Research Fellow and all the pathologists participating in the trial.

The Pathology Committee will be responsible for agreeing the pathology guidelines at the beginning of the trial. It will then meet regularly to receive feedback on recruitment rates and discuss problems arising with the protocol.

Data Monitoring Committee

The Data Monitoring Committee will be responsible for the interpretation of the interim analysis and for monitoring the accumulating data. The Data Monitoring Committee will also oversee the monitoring of the quality of the surgery and pathology in the trial, making recommendations about action to be taken if problems are identified.

Steering Group

Chair: Professor PJ Guillou

The Steering Group will consist of Professor PJ Guillou, the Research Fellow, Professor N Bosanquet, Mrs J Brown (Statistician), Dr P Franks, Dr SA Haining (Research Manager), Dr P Quirke, and Mrs M Stead (Senior Trial Co-ordinator). The Steering Group will be responsible for the publicity of the trial, for queries about patient management and for interpretation of the results. The YCTRU will co-ordinate and provide administration for the Steering Group.

Research Fellow

The Research Fellow will be the key contact between the participating centres and the main co-ordinating centre.

14. ETHICAL CONSIDERATIONS

The trial must be approved by the appropriate ethics committee of each participating institution prior to its entry into the study.

Informed written consent will be obtained from the patients prior to randomisation into the study (see Appendix 6 for suggested patient information leaflet). The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his or her further treatment.

15. ONGOING PROTOCOLS

There are several important trials ongoing in the area of colorectal cancer which need to be taken into consideration in the design of this trial.

The issue of patients being entered into AXIS and/or QUASAR as well as this trial has been partly covered in Section 6, Adjuvant Therapy. It is important to ensure that if patients are entered into this trial and AXIS or QUASAR that the data collection procedures for either of the trials do not interfere with the other. However, the information required for both AXIS and QUASAR is minimal and they require very little data on the operation performed. It is envisaged therefore that collection of the main trial data for patients in both trials will not present a problem for participants. The detailed collection of quality of life and health economic data in this trial and in QUASAR on the other hand, could present problems. The QUASAR organisers plan to randomly sample trial participants to be involved in this detailed study. They have agreed not to include patients entered into the CLASICC Trial in their sampling frame so as to avoid the same patients being asked for detailed information twice. The QUASAR and AXIS trials offices will also be flagging their patients with the Office for National Statistics in order to supplement their long-term follow-up. The YCTRU will send regular lists of all patients entered into this trial to the QUASAR and AXIS offices in order to check whether patients are already flagged with the Office for National Statistics, and to avoid duplication of quality of life data collection.

There is also a National Institute of Health ongoing trial of laparoscopic-assisted colectomy versus open colectomy for colon cancer in the United States (US trial). The US trial and the potential for collaboration with this trial has already been discussed in Section 10.

16. FINANCE

Payment of £50 per patient will be made to the surgeons to cover minor administrative costs and enable centres to identify a key worker to assist in the quality of life data collection.

Payment of £51.17 per pathology specimen will be made to cover the pathologists' additional time, and the production of an extra set of slides and photographs of the specimen.

17. INDEMNITY

Since this trial is sponsored by the Medical Research Council, please refer to Appendix 7 for the MRC statement with regard to indemnity.

18. PUBLICATION

Publication will be on behalf of the MRC CLASICC Trial. Participants will be appropriately recognised in the final publications.

19. REFERENCES

- Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ *et al* (1994)
Role of circumferential margin involvement in the local recurrence of rectal cancer
Lancet 344, 707-711
- Aaronson NK, Ahmedzai S, Bullinger M, Crabeels D, Estape J *et al* (1991)
The EORTC core quality of life questionnaire: interim results of an international field study
In Osoba D (ed) 'Effect of cancer on quality of life' CRC Press, pp 185-203
- Attwood SEA, Hill ADK, Murphy PG, Thornton J, Stephens RB (1992)
A prospective randomised trial of laparoscopic versus open appendectomy
Surgery 112, 497-501
- Cirocco WC, Schwartzman A, Golub RW (1994)
Abdominal wall recurrence after laparoscopic colectomy for colon cancer
Surgery 116, 842-846
- Clair DG, Lautz DB, Brooks DC (1993)
Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma surgery
Surgery 113, 355-388
- Dean PA, Beart RW, Nelson H, Elftmann TD, Schlinkert RT (1994)
Laparoscopic-assisted segmental colectomy: early Mayo Clinic experience
Mayo Clinic Proc. 69, 834-840
- Dempster AP, Laird NM, Rubin DB (1972)
Maximum likelihood from incomplete data via the expectation maximisation algorithm
J R Stat Soc B39, 1
- Elftmann TD, Nelson H, Ota DM, Pemberton JH, Beart RW (1994)
Laparoscopic-assisted colectomy: surgical techniques
Mayo Clin Proc. 69, 825-833
- EuroQol Group (1990)
EuroQol - a new facility for the measurement of health-related quality of life
Health Policy 16, 199-208
- Fligelstone LJ, Johnson RC, Stiff GJ, Wheeler MH (1993)
Laparoscopy and gastrointestinal cancer (letter)
Am J Surg 166, 571
- Franklin ME, Ramos R, Rosenthal D, Schuessler W (1993)
Laparoscopic colonic procedures
World J Surg 17, 51-56

- Gelber RD, Goldhirsch A (1986)
 A new endpoint for the assessment of adjuvant therapy in post-menopausal women with operable breast cancer.
J Clin Oncol 44, 1772-1779
- Goldhirsch A, Gelber RD, Simes RJ, Glasziou P, Coates AS (1989)
 Costs and benefits of adjuvant therapy in breast cancer; a quality adjusted survival analysis.
J Clin Oncol 7, 36-44
- Goodman D, Irvin TT (1993)
 Delay in the diagnosis and prognosis of carcinoma of the right colon
Br J Surg, 80, 1327-1329
- Guillou PJ, Darzi A, Monson JRT (1993)
 Experience with laparoscopic colorectal surgery for malignant disease
Surg Oncol 2, Suppl 1: 43-39
- Guillou PJ (1994)
 Laparoscopic surgery for diseases of the colon and rectum - quo vadis?
Surg Endosc 8, 669-671
- Jatzko G, Lisborg P, Wette V (1993)
 Improving survival rates for colorectal cancer
Br J Surg 79, 588-491
- Lewis C, Darzi A, Goldin R, Menzies-Gow N, Guillou PJ, Monson JRT (1993)
 Laparoscopic abdominoperineal resection of the rectum: assessment of adequacy of excision
Br J Surg 80, 846
- MacFarlane JK, Ryall RD, Heald RJ (1992)
 Mesorectal excision for rectal cancer
Lancet 341, 457-460
- MacIntyre IMC (1992)
 Laparoscopic herniorrhaphy
Br J Surg 79, 1123-1124
- Mantel N, Haenszel W (1959)
 Statistical aspects of the analysis of data from retrospective studies of disease
J Nat Cancer Inst 22, 719-748
- McArdle CS, Hole D, Hansell D, Blumgart LH, Wood CB (1990)
 Prospective study of colorectal cancer in the West of Scotland: 10-year follow-up
Br J Surg 77, 280-282

- Miller R, Roe AM, Eltringham WK, Espiner HJ (1992)
Laparoscopic fixation of sigmoid volvulus
Br J Surg 79, 435
- Monson JRT, Darzi A, Carey PD, Guillou PJ (1992)
Prospective evaluation of laparoscopic assisted colectomy in an unselected group of patients
Lancet 340, 831-833
- Murray GD (1995) Personal correspondence addressed to Damien McElvenny
- Musser DJ, Boorse RC, Madera F, Reed JF (1994)
Laparoscopic colectomy: at what cost?
Surgical Laparoscopy & Endoscopy 4, 1-5
- Neugebauer E, Troidl H, Spangenberg W, Dietrich A, Lefering R *et al*
The Cholecystectomy Group (1991)
Conventional versus laparoscopic cholecystectomy and the randomised controlled trial
Br J Surg 78, 150-154
- Nezhat F, Nezhat C, Pennington E (1992)
Laparoscopic proctectomy for infiltrating endometriosis of the rectum
Fertility & Sterility 57, 1129-1132
- O'Rourke NA, Heald RJ (1993)
Laparoscopic surgery for colorectal cancer
Br J Surg 80, 1129-1230
- Pappas TN (1992)
Laparoscopic colectomy - the innovation continues
Ann Surg 216, 701-201
- Peters WR, Bartels TL (1993)
Minimally invasive colectomy: are the potential benefits realized?
Dis Colon and Rectum 36, 751-756
- Phillips RKS, Hittinger R, Blesovsky L, Fry JS, Fielding LP (1984 a)
Large bowel cancer: surgical pathology and its relationship to survival
Br J Surg 71, 604-610
- Phillips RKS, Hittinger R, Blesovsky L, Fry JS, Fielding LP (1984 b)
Local recurrence following curative surgery for large bowel cancer: the overall picture
Br J Surg 71, 12-16
- Phillips EH, Franklin M, Carroll BJ, Fallas MJ, Ramos R, Rosenthal D (1992)
Laparoscopic Colectomy
Ann Surg 216, 703-707
- Quirke P (1995) Personal correspondence addressed to Damien McElvenny

- Quirke P, Dixon MF (1988)
The prediction of local recurrence in rectal adenocarcinoma by histopathological examination
Int J Colorect Dis 3, 127-131
- Quirke P, Durdey P, Dixon MF, Williams NS (1986)
Local recurrence of rectal adenocarcinoma due to inadequate surgical resection
Lancet ii, 996-999
- Ramos JM, Gupta S, Anthone GJ, Ortega AE, Simons AH, Beart RW (1994)
Laparoscopy and colon cancer: is the port site at risk?
Arch Surg 129, 897-899
- Sackier JM, Berci G, Hiatt JR, Hartunian S (1992)
Laparoscopic abdominoperineal resection of the rectum
Br J Surg 79, 1207-1208
- Sprangers MAG, Gill A, Bjordal K, Groenvold M, Aaronson (1993)
The European Organisation for research and treatment of cancer approach to quality of life assessment. Guidelines for developing questionnaire modules
Quality of Life Research 2, 287-95
- Sprangers MAG (in preparation)
- Tate JJ, Kwok S, Dawson JW, Lau JY, Li AKC (1993)
Prospective comparison of laparoscopic and conventional anterior resection
Br J Surg 80, 1396-1398
- Torrance GW (1987)
Utility approach to measuring health related quality of life
J Chron Dis 40, 593-600
- UK Co-ordinating Committee on Cancer Research (1989)
Clinico-pathological staging booklet
UKCCCR
- Van Ye T, Cattet RP, Henry LG (1994)
Laparoscopically assisted colon resections compare favourably with open technique
Surgical Laparoscopy & Endoscopy 1, 25-31
- Wexner SD, Johansen OB, Noguera JJ, Jagelman DG (1992)
Laparoscopic total colectomy
Dis Colon and Rectum 35, 651-665
- Zwinderman AM (1992)
Statistical analysis of longitudinal quality of life data with missing measurements
Quality of Life Research 1, 219-224

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. Pathologists must state their method of fixation/tension and not change. Once fixed, the anterior and posterior aspect of the specimen should be photographed with a cm scale and then two 2 cm x 2 cm colour slides should be produced.

Macroscopic examination

After fixation (at least 3 days), the peritoneal reflection is identified and the relative position of the tumour recorded, ie. 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 Bouin's fixative or 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 2 cm 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 2 cm x 2 cm colour slide is produced. Both the macroscopic and the sliced tumour colour photographs and slides should be sent to the YCTRU, labelled with the hospital, surgical number and trial number.

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 (Fig 1); 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 (Fig 2). 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.

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

Figure 1



Measurement of spread: distance of maximal tumour spread from the muscularis propria. This can either be to the edge of the primary tumour (A) or to a metastasis (B).

Figure 2



Measurement of CRM margin: distance from the tumour to the circumferential margin measured from the closest point. This can either be from the primary tumour (A) or from a metastasis (B). The closer one should be used.

Lymph nodes

Any metastatic deposit > 3mm 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. A minimum of eight lymph nodes should be aimed for.

The C2 node is the node of the high tie closest to the tumour. The pN3 lymph nodes lie along the inferior mesenteric artery and superior rectal artery prior to bifurcation into the left and right superior rectal arteries. If the apical lymph node is involved, the tumour stage is also pN3.

Histology

Levels on a block may be required if tumour is close (<5 mm) to a margin. Involvement is defined as tumour 1 mm 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 microscope stage. 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, ie. 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 necessary if definite peritoneal involvement is not shown.

Method for dissection of colonic 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 macroscopic photographs a second set of haematoxylin and eosin sections, apart from the original diagnostic sections which are retained by the laboratory, should be sent to the YCTRU. Central review of the histology will be performed to audit the pathology. Pathologists should indicate which haematoxylin and which eosin slide is diagnostic of CRM involvement or peritoneal involvement if it is present.

It would be appreciated if two pieces of tumour and one piece of normal mucosa could be taken and blocked. These should be sent with photographs to the YCTRU. 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 CLASICC Trial.

APPENDIX 2

ELIGIBILITY CHECKLIST

To be completed by the clinician prior to telephoning the YCTRU for randomisation. A copy of the checklist is to be sent to the YCTRU. The checklist will include simple yes/no tick boxes to the following questions. Shading will be used to indicate when a patient is ineligible.

- Does the patient have clinical diagnosis of colorectal cancer (based on colonoscopy or barium enema undertaken within 30 days of intended date of surgery)?
- Is the patient suitable for elective surgical resection by right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection or abdomino-perineal resection?
- Does the patient have a tumour of the transverse colon?
- Has the patient any contraindication to pneumoperitoneum such as severe cardiovascular disease?
- Does the patient have an acute large bowel obstruction?
- Has the patient had any other malignancy within previous five years (except basal cell carcinoma, *in situ* carcinoma of cervix or prostate cancer)?
- Does the patient have associated gastro-intestinal diseases that require surgical intervention, ie. Crohn's, chronic ulcerative disease, familial polyposis?
- Does the patient have synchronous, multiple tumours?
- If patient is female, is she pregnant?
- Is date of planned surgery not more than 28 days after randomisation?

A reminder of the information that will be required to randomise a patient over the telephone will be provided on the checklist form.

APPENDIX 3

WHO GRADES OF PERFORMANCE STATUS

Grade	Summary	Description of performance status
0	Normal	Able to carry out all normal activity without restriction
1	With effort	Restricted in physically strenuous activity; ambulatory, can do light work
2	Restricted	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Dependent	Capable of only limited self-care; confined to bed or chair for more than 50% of waking hours
4	Immobile	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

APPENDIX 4

ASA GRADES

- I healthy patient
- II one systemic, well-controlled disease
- III multiple system disease or well-controlled major system disease

APPENDIX 5

LIST OF PARTICIPANTS

<i>Surgeon</i>	<i>Pathologist</i>	<i>Hospital</i>
Mr D Bartollo MS FRCS	Dr H Gilmore	The Royal Infirmary, Edinburgh
Mr T Brennan FRCS	Dr J Wyatt	St James's University Hospital, Leeds
Mr D Carey MCh FRSCI FCS (HK)	To be allocated	University Hospital of Wales, Cardiff
Mr A Darzi MS FRCS FRCSI	Dr R Golding	St Mary's Hospital, London
Professor PJ Guillou BSc MD FRCS	Dr J Wyatt	St James's University Hospital, Leeds
Mr M Hershman MS MSc FRCS	Dr J Nash	Royal Liverpool Hospital, Liverpool
Mr R Kapadia MS FRCS	Dr R Pyrah	Airedale General Hospital, Keighley
Professor JRT Monson MD FRCS	Dr A McDonald	Castle Hill Hospital, North Humberside
Mr P Sagar Bsc MD FRCS	Dr J Wyatt	Leeds General Infirmary, Leeds
Mr J Scholefield MB ChB FRCS CHM	Dr D Jenkins	Queens Medical Centre, Nottingham
Mr H J Scott MS FRCS	Dr M Hall	St Peter's Hospital, Chertsey
Mr N Scott MD FRCS	Dr G Armstrong	Hope Hospital, Salford
Mr S Shimi FRCS	Dr D Hopwood	Ninewells Hospital, Dundee
Mr R Steele MS FRCS	Dr D Jenkins	Queens Medical Centre, Nottingham
Mr J Stewart MD FRCS (Ed) FRCS (Eng)	To be allocated	Manor Hospital, Walsall
Mr M G Thomas Bsc MS FRCS	To be allocated	Bristol Royal Infirmary, Bristol
Mr JS Varma MD FRCS	Dr M Bennett	Royal Victoria Infirmary, Newcastle
Mr J Wellwood MChir FRCS	Dr R Owen	Whipps Cross Hospital, London

APPENDIX 6

PATIENT INFORMATION LEAFLET

A Trial of Laparoscopic Surgery Versus Conventional Open Surgery For Colorectal Disease

This sheet is to help explain some of the research we are doing and ask you if you would like to take part in it.

Operations for colorectal disease are usually carried out by conventional open surgery through an abdominal incision. The recent development of specialist instruments have made it possible to carry out this type of operation laparoscopically. A laparoscope is a special type of tube which is put into your abdomen through which special instruments can be used to carry out the operation. The surgeon uses small cameras to watch on television screens exactly what is going on inside your abdomen during the operation. In the laparoscopic surgery the cut needed to remove the section of diseased bowel is much smaller than that required for the more usual operation. Although the operation may take longer than conventional open surgery it may have the benefit of reducing the time you need to stay in hospital and enable you to return to work/normal activity more quickly and with fewer complications. We are not sure how effective the laparoscopic surgery is in relation to conventional open surgery and so we are conducting the trial to see if laparoscopic surgery is at least as effective and safe as the more usual open surgery.

This trial is a randomised trial; in this kind of trial, people are allocated randomly to one of two treatment methods. In our trial the same operation will be performed by either laparoscopic surgery or the more usual open surgery. 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 possible, he will convert the procedure to a conventional open operation.

As part of this trial we will be monitoring your progress very closely. You will be asked to complete some questionnaires about how you feel. This will be simple to do and will help us to see the effect of your operation on how you feel and on the time it takes you to recover.

All the surgeons taking part in this research have experience of performing operations for colorectal disease laparoscopically and through the more usual conventional open procedure.

The proposed trial has been discussed and agreed by a number of experienced colorectal surgeons throughout the United Kingdom, and a detailed written document describing the trial has been prepared. The procedures laid down in this document have been accepted for use in this hospital by the local research ethics committee. These committees were set up to make sure that the safety and wellbeing of the patient comes first in any research carried out.

If you do not want to take part in the trial you do not have to tell us why, although giving a reason might help the research. If you are happy to take part in this trial, you will be asked to sign a consent form to show that you have understood what it is about and what is involved. You can change your mind and withdraw from the trial at any time. If you refuse to take part or decide to withdraw, your treatment will not be affected, nor will your relationship with your doctor.

APPENDIX 7

MRC STATEMENT IN REGARD TO INDEMNITY

When problems or queries are addressed to us, our practice has been to respond as follows:

The MRC as sponsor of a trial or work involving human subjects accepts liability attached to its sponsorship of the work, and as such would give sympathetic consideration to claims for any non-negligent harm suffered by a human subject as a result of participating in the work. (This would not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial - see also next paragraph.) Like other publicly funded bodies, the Council is unable to insure and thus cannot offer advance indemnity cover for subjects participating in MRC-funded studies.

Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within that hospital, whether or not that patient is participating in an MRC-supported study. There the MRC does not accept liability for negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not, and the MRC cannot be held liable for any breach in the hospital's duty of care.