# The M.E.R.C.U.R.Y Project.

# Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study.

PROTOCOL

October 2001

**Study number**: Mercury 1.

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# 1. LIST OF COLLABORATORS.

| Hospital | Name | Occupation |
|---|---|---|
| | | |
| **1. Leeds General Infirmary** | Paul Finan | Surgeon |
| | Peter Sagar | Surgeon |
| | Dermot Burke | Surgeon |
| | Alan Chalmers | Radiologist |
| | Phil Quirke | Pathologist |
| | Mr K Sasapu | Research Fellow |
| | Alison Cairns | Pathologist |
| | David Sebag-Montefiore | Oncologist |
| | Diane Jones | Nurse Specialist |
| | Dr M Seymour | Oncologist |
| | Ms N Chauhan-Lall | YCRN Trials Co |
| **2. St. James, Leeds** | Simon Ambrose | Surgeon |
| | Mr I Botterill | Surgeon |
| | Mr D Jayne | Surgeon |
| | Ashley Guthrie | Radiologist |
| | Nigel Scott | Pathologist |
| | | Oncologist |
| | Jill Bisset | Nurse Specialist |
| | Dr C Verbeke | Pathologist |
| **3. Llandough Hospital** | Andrew Radcliffe | Surgeon |
| | Mr J Torkington | Surgeon |
| | Dr R Bleehen | Radiologist |
| | Mike Bourne | Radiologist |
| | Nick Dallimore | Pathologist |
| | Tim Maughan | Oncologist |
| | Yvette Pearson | Nurse Specialist |
| **4. Ashford St Peters** | Douglas Donaldson | Surgeon |
| | Humphrey Scott | Surgeon |
| | Phil Bearn | Surgeon |
| | Mike Creagh | Radiologist |

| | | |
|---|---|---|
| | Sue Dodds | Pathologist |
| | Gary Middleton | Oncologist |
| | Lynne De Snoo | Nurse Specialist |
| **5. Epsom General Hospital** | Paul Toomey | Surgeon |
| | Ashraf Raja | Surgeon |
| | Chris George | Radiologist |
| | Louis Temple | Pathologist |
| | David Cunningham | Oncologist |
| | Sheena Woodward | Nurse Specialist |
| **6. Mayday, Croydon** | Ian Swift | Surgeon |
| | Nicola Bees | Radiologist |
| | Helena Blake | Radiologist |
| | N Jeyadeven | Radiologist |
| | Abed Arnaout | Pathologist |
| | David Cunningham | Oncologist |
| | | Nurse Specialist |
| **7. Frimley Hospital** | Mark Gudgeon | Surgeon |
| | David Edwards | Surgeon |
| | Simon Mellor | Surgeon |
| | Hassan Massiuh | Radiologist |
| | Mona Elmahallawy | Pathologist |
| | Gary Middleton | Oncologist |
| | Katherine Bundy | Nurse Specialist |
| **8. Basingstoke** | Prof Heald | Surgeon |
| | Brendon Moran | Surgeon |
| | Delia Peppercorn | Radiologist |
| | Jenny Finch | Pathologist |
| | Ian Ilesley | Pathologist |
| | Dr G Sharpe | Oncologist |
| | Mr DM Gold | Surgeon |
| | Mr TD Cecil | Surgeon |
| | Geoff Sharpe | Oncologist |
| | Ann Leppington-Clarke | Nurse Specialist |
| **9. Karolinska, Stockholm** | T Holm | Surgeon |
| | L Blomquist | Radiologist |
| | Dr M Torkzad | Radiologist |
| | Dr J Lindholm | Pathologist |
| | Prof B Glimelius | Oncologist |
| | Ms B Andersson | Nurse Specialist |
| | Ms Y Ericsson- Alm | Nurse Specialist |

| | | |
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| **10. Berlin** | J Strassburg | Surgeon |
| | Petra Knuth | Radiologist |
| | Volker Loy | Pathologist |
| | Prof Hellriegel | Oncologist |
| | Dr Katja Ludwig | Nurse Specialist |
| **11.The Norwegian Radium Hospital. Oslo, Norway** | Dr J Wiig | Surgeon |
| | Dr S Larsen | Surgeon |
| | Dr T Vetrhus | Radiologist |
| | Dr H Emblemsvaag | Radiologist |
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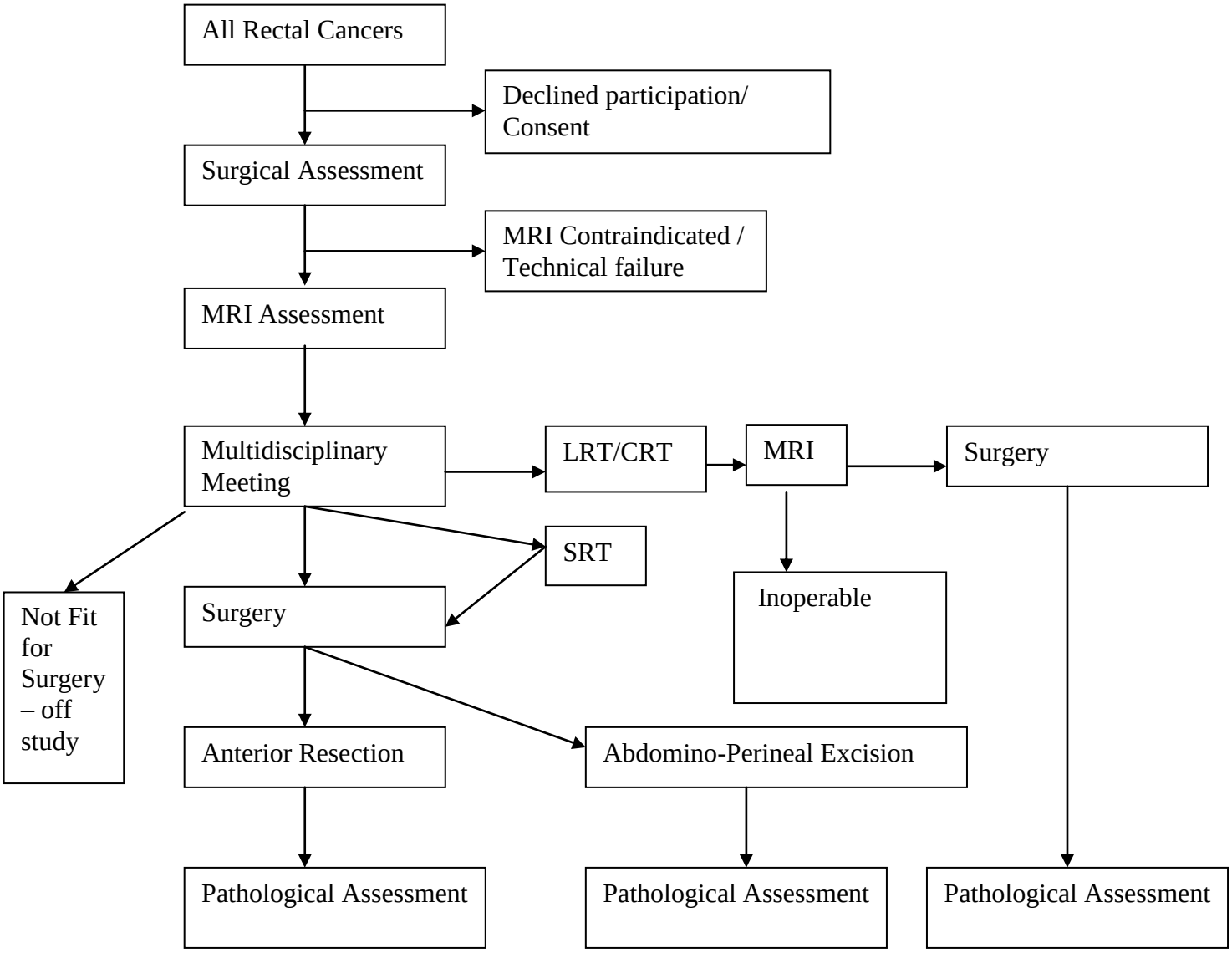
| **Royal Marsden Hospital** | Gina Brown | Radiologist |
| **Royal Marsden Hospital** | Andy Norman | Statistician |
| **Royal Marsden Hospital** | Andrew Wotherspoon | Pathologist |
| | Prof D Cunningham | Medical Oncologist |
| | Dr M Hill | Medical Oncologist |
| | Dr P Ross | Medical Oncologist |
| | Dr D Tait | Clinical Oncologist |
| | Ms A Massey | Nurse Specialist |

## 3. OUTLINE OF THE STUDY

All patients with primary rectal cancer will be approached




This group will form the basis of the MRI and histopathological equivalence study

This group will allow descriptive study of MRI assessment of those tumours encroaching the anal canal

This group will allow a descriptive assessment of the MRI appearance after neo-adjuvant therapy and comparison with path

**Primary endpoint: To Demonstrate Equivalence of MRI and Histopathological Assessment of Extramural Depth of Tumour Spread.**

# 4. INTRODUCTION

## 4.1 Aims of the Study

The validated rectal cancer-staging systems (such as TNM and Dukes' classification) currently in clinical practice are based on the findings from the excised specimen. With the change towards pre-operative radiotherapy, it is urgent that a pre-operative staging system be developed on which a treatment plan could be based [1].

Small single centre studies have shown promising results using high-resolution pelvic phased-array body-coil magnetic resonance imaging (MRI) These studys have provided sufficient information to suggest that high-resolution pelvic phased-array body-coil magnetic resonance imaging (MRI) of a rectal cancer we can demonstrate equivalence to the histopathological assessment of the excised specimen however these studys were based on small numbers of patients.

There is therefore a need for a large prospective study; to demonstrate that high quality MRI can be produced in a multicentre setting, to allow correlation with clinical findings that are prospectively recorded and a need to standardise the pathology and ensure high quality TME surgery.

The long-term aim of this collaborative is the development of a Pre-Operative MRI-based Staging System (P.O.M.S.S.) for rectal cancer that will give an accurate and reproducible assessment of prognosis towards local recurrence risk and overall five-year survival. The development of this staging system would allow more accurate assessment of chemo-therapeutic and radio-therapeutic based regimes used in the treatment of advanced rectal cancer.

## 4.2 Primary Aim

- To Demonstrate Equivalence of MRI and Histopathological Assessment of Extramural Depth of Tumour Spread.

## 4.3 Secondary Aims

- An audit of Total Mesorectal Excision (TME) based on specimen grade as defined by Quirke et al.

- An audit of Abdomino-Perineal Excision rates in multiple centres.

- The correlation between outpatient and on-table assessment of tumour height.

- An audit of the quality of surgery based on tumour height.
- Development of a Surgical Assessment Technique for excision of a low rectal cancer based on pelvimetry, assessment of the mesorectal size and tumour height.
- Inter- and intra-observer variation in the reporting of MRI of the rectum
- To study the assessment of MRI in the staging of tumours encroaching the anal canal.
- Assessment of the circumferential resection margin (CRM) positivity rate.
- To study MRI in the assessment of tumour response after neo-adjuvant therapy.
- The reproducibility of high-resolution pelvic phased-array body-coil magnetic resonance imaging (MRI) in multiple centres.
- The assessment of the sphincter-sparing distance and prediction of feasibility of an Abdomino-Perineal Excision (APE) or a Low Anterior Resection (LAR).
- Assessment of the distance to the Circumferential Resection Margin (CRM) for tumour, nodes or deposits.
- Assessment of extra-mural venous invasion (vessels >3mm diameter)
- Assessment of mesorectal nodes (>3mm focus)
- Assessment of the peritoneal reflection on MRI for macroscopic or microscopic involvement of tumour.
- Identification of the peritoneal reflection on MRI
- Comparison of extra-mural deposits of tumour with histopathology.
- A correlation of extra-mural morphology with tumour differentiation
- An audit of detailed pathological assessment of rectal cancers
- Development of a Tissue Bank for further molecular-bases tissue research
- An audit of current Oncological practice in 10 centres

## 4.4 References

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# 5. BACKGROUND TO THE STUDY

## 5.1 Scientific Rationale for the Study

A prime concern for the clinician treating rectal cancer is the avoidance of local recurrence. This causes severe morbidity for the patient from pelvic pain, ureteric obstruction, fistulation and poor bowel function. Five-year survival in patients with local recurrence is less than 5% with a median survival of only seven months [1,2]. Many patients will die with local recurrence being the only manifestation of their tumour and palliation is often difficult to achieve [3]. In these patients our surgical treatment has failed and that failure may be attributed to the surgeon.

At present histopathological analysis of the surgical specimen provides important information regarding the prognosis for the patient. This influences the use of post-operative adjuvant therapy for patients with poor prognostic features. However, pre-operative knowledge of these prognostic indicators could influence both the use of pre-operative adjuvant therapy and aid the selection of the most appropriate surgical approach. Depth through and beyond the bowel wall remains an important method of predicting survival. However, the presence of poor prognostic indicators within each TNM stage permits identification of sub-groups of patients who are at different risks of recurrence and who should therefore be treated more or less intensively. The challenge is to identify such patients before surgery in order to provide additional treatment in the hope of providing a better outcome than surgery alone. Many clinico-pathological prognostic factors have been studied, but the important independent pathological prognostic factors are: the depth of tumour involvement of the bowel wall (the T component of the TNM classification), extent of extramural spread, nodal status, extramural venous invasion by tumour, tumour involvement of the circumferential margin and peritoneal perforation by tumour [4].

Recent articles in the literature have suggested that MRI staging can improve the outcome in rectal cancer by the identification of tumour invasion in relation to the mesorectal fascia. If the resectibility can be predicted from pre-operative staging then the need for pre-operative therapy could be targeted at those patients with the highest risk of the development of local recurrence [5].

It has been shown in single centre series that the extent of extramural invasion shows direct agreement with histopathological measurements [6]. If this can be expanded to assess other factors such as the relationship to the circumferential margin, extra-mural venous invasion, nodal disease and this could be confirmed by a study assessing the equivalence between MRI and the Histopathology, then a Pre-Operative Staging System may be developed.

The need for improved pre-operative assessment is confirmed in light of recent research into the effect of using pre-operative radiotherapy. The superiority of pre-operative over post-operative radiotherapy was shown in 1985 and it was suggested that pre-operative therapy would approximately halve the risk of local recurrence rate in any given group at risk [7]. Today both radiotherapy and chemotherapy have been used to reduce the local recurrence rate and improve survival but the efficacy of both techniques remains controversial [8]. This led to

the consensus that irradiation reduced local recurrence but the survival benefit remained unproven.

However, neo-adjuvant radiotherapy is not without associated morbidity. A recent audit performed in the North Trent Region (UK) showed a higher than expected anastomotic leak rate (15%) and perineal wound infection rates (18%) following the introduction of pre-operative radiotherapy. The need to avoid a delay between radiotherapy and surgery highlighted the increased rate of wound breakdown. The increased anastomotic leak rate can be compared to a previous Trent Audit and thus the rates experienced by the same surgeons before the introduction of radiotherapy, although a selection bias may have been incurred with more low anastomoses being performed [(9)].

Much of the evidence for the benefit of pre-operative radiotherapy comes from the Swedish Rectal Cancer Trials. In 1988, a meta-analysis of the then currently available randomised trials failed to show an overall significant effect of pre-operative radiotherapy on mortality [(10)]. More recently the results of published trials remain inconsistent and a further meta-analysis was performed in 2000. This concluded that in patients with resectable rectal cancer pre-operative radiotherapy significantly improved overall and cancer-specific survival compared with surgery alone [(11)]. However, the irradiation schedules used varied greatly between trials, histological staging of patients undergoing radiotherapy was not accurate and overall complications in the immediate post-operative period were significantly increased. By excluding the Swedish data from this meta-analysis there is loss of significance for overall improvement. Indeed many of the surgeons in the Swedish trials who operated on patients with rectal cancer were not sub-specialized in colorectal surgery and performed few operations and very few adopted TME. Also in the Swedish trials the high rate of potentially curative resections may be explained by the eligibility criteria, which excluded emergency cases and patients with pre-operative signs of distant metastases and/or irresectable tumours. The Swedish Rectal Cancer Trial showed a relative survival benefit of 21%, which gave an increase in the 5-year survival from 48-58% and a reduction in local recurrence from 27 –11%. This would suggest that the benefits of adjuvant radiotherapy in reducing local recurrence seem to be dependent on a high local recurrence rate for surgery alone. With local recurrence rates of less than 10%, there is no data demonstrating a beneficial effect with the addition of radiotherapy [(12)]. This would mean that in order to further reduce local recurrence many patients would need to be treated to achieve a significant further reduction [(13)].

The recently published Dutch Study suggests that all patients with curable rectal cancer can benefit from the addition of short-course neo-adjuvant. This trial's main weaknesses have to be the selection bias performed in the definition of resectable disease and the high rate of abdomino-perineal excisions [(14)]. This study demonstrated that short course preoperative radiotherapy does not significantly reduce the risk of local recurrence in patients who have a positive circumferential resection margin and the logical conclusion is that MRI may allow better selection of patients.

Numerous studies have reported local recurrence rates ranging from 3.7 – 50% depending on the length of follow-up and the number of patients in the study

[15,16,17,18,19,20]. These wide ranges of local recurrence in the literature suggest that surgical factors do affect outcome [21]. Studies have suggested that the individual surgeon is an independent prognostic factor influencing the risk of post-operative mortality and morbidity, local recurrence rate and survival [22,23,24]. Indeed many approaches have been used in an attempt to reduce local recurrence. These include Total Mesorectal Excision (TME); total pelvic lymphadenectomy and rectal stump irrigation with cytocidal agents. Of these, the introduction of the technique of Total mesorectal Excision (TME) has improved the local recurrence rate from surgery alone. Units in which this technique has been taught have seen corresponding improvements [25].

It is well recognised that pathological examination of the circumferential resection margin (CRM) can predict patients at high risk of local recurrence due to residual microscopic disease. The involvement of the CRM is independent of Dukes' stage, and both are important prognostic factors. *Quirke et al* demonstrated that in 36% of patients who the surgeon felt had all microscopic tumour removed, there was involvement of the CRM with a subsequent local recurrence rate of 64%. However, in the 64% of patients with a clear (uninvolved) CRM the local recurrence rate was 9% [26]. The use of an involved CRM accurately predicted by MRI would serve as a selection criterion for neo-adjuvant therapy.

Current practice for the management of rectal cancer varies throughout the United Kingdom and Europe. There is no clear pre-operative objective, reproducible, validated staging system, either radiological, surgical or pathological to accurately stage the outcome of rectal cancer. Whilst some units are using MRI staging of tumours, these findings need to be accurately correlated to the histopathological findings by standardised methodology. Individual factors relating to the tumour, especially its relationship to the mesorectal fascia needs to be assessed. Clearly staging the tumour and using the surgical technique of TME in some patient's may avoid the use of neo-adjuvant therapy and more appropriate selection of patients for neo-adjuvant therapeutic regimes.

A further benefit of this trial would be in patients with advanced disease where treatment protocols are limited by the lack of prognostic information from tumour assessment in the pre-operative phase. Indeed tumour response is difficult to quantitatively assess without clear pre-operative prognostic information.

Unlike recent studies assessing the treatment of rectal cancer we aim to include all newly diagnosed rectal cancers so that there is no selection bias. With accurate standardised surgical assessment of these tumours correlations may be made. This study will also act as an audit of current practice in the included centres.

## 5.2 This Studies Relationship to Current Practice

As the study involves unselected cases of rectal cancer,it is expected that clinical practice would proceed in the normal way. All of the enrolled centres currently take the MRI findings into account in their clinical decision making process. It is important to clarify that this study is not designed to alter their clinical decision making process. It is expected that patients will be discussed in the setting of the multidisciplinary team meeting, where both the clinical findings and the MRI

findings and the MRI findings are discussed, and decisions made concerning the use, or not, of pre-operative radiotherapy.

Patients will be considered for entry into current clinical trials, such as CRO-7 or EXPERT trials, and they would be free to participate in the normal way and this study would not interfere with this process.

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# 6. STUDY DESIGN

## 6.1 Rationale For The Design Of This Trial

The recently published Dutch Rectal Cancer Trial suggests that all patients with curable rectal cancer should undergo pre-operative short-course radiotherapy. However, single-centre studies have shown the value of high-resolution pelvic phased-array body-coil MRI in the staging of rectal cancer.

We believe that radiotherapy can be targeted to individual patients by the accurate pre-operative assessment of rectal cancer by the use of MRI. By comparing the imaging and the histopathological specimen along the lines of resection of the tumour equivalence of the techniques can be performed. Once the techniques have been shown to be reliable and reproducible a follow-up study is planned to assess outcomes, i.e. survival and local recurrence rate.

## 6.2 Design Overview

This study will be a prospective, multi-centre observational study. All patients diagnosed with rectal cancer in the enlisted centres will be eligible for inclusion and would be approached. By using all patients we would exclude a selection bias towards the better prognostic cases. There will be no alteration of current diagnostic or treatment protocols in the participating centres.

## 6.3 Enrolment to the Study

All patients with rectal cancer are to be invited to take part in the study. Patients will have the purpose of the study, study procedures and their responsibilities fully explained and written informed consent obtained before any study related procedures are undertaken.

Each patient will receive a patient information sheet (an example is given in Appendix 1) prior to signing informed consent. Informed consent will be obtained.

Further information will be available through The Pelican Centre, the Research Fellow, and local Colorectal Nurse Specialists.

**The aim is to have a minimum of at least 90% of all newly diagnosed elective rectal cancer patients registered for the trial.**

## 6.4 Study Visits

### 6.4.1 Patients

Individual patients will not be visited. However, a central phone number will be available for patients to contact for information (01256 314746).

Depending upon local policy some patients will be consenting to life-long indirect follow-up, via their own surgical consultant and using the NHS Central Register (which is part of the Office for National Statistics) to identify deaths. No extra outpatient assessment will be required.

### 6.4.2 Centres

All centres will be visited regularly for data collection purposes and all investigators will have access to the study coordinators. Facsimile services and a telephone answering machine will be provided for the submission of patient registration forms.

It is hoped that the use of the NHS Intranet will allow easier collection of data and reduce the number of centre visits.

The study will rely upon the integrity of the individual centres to enrol all patients with rectal cancer.

### 6.4.3 Coordination

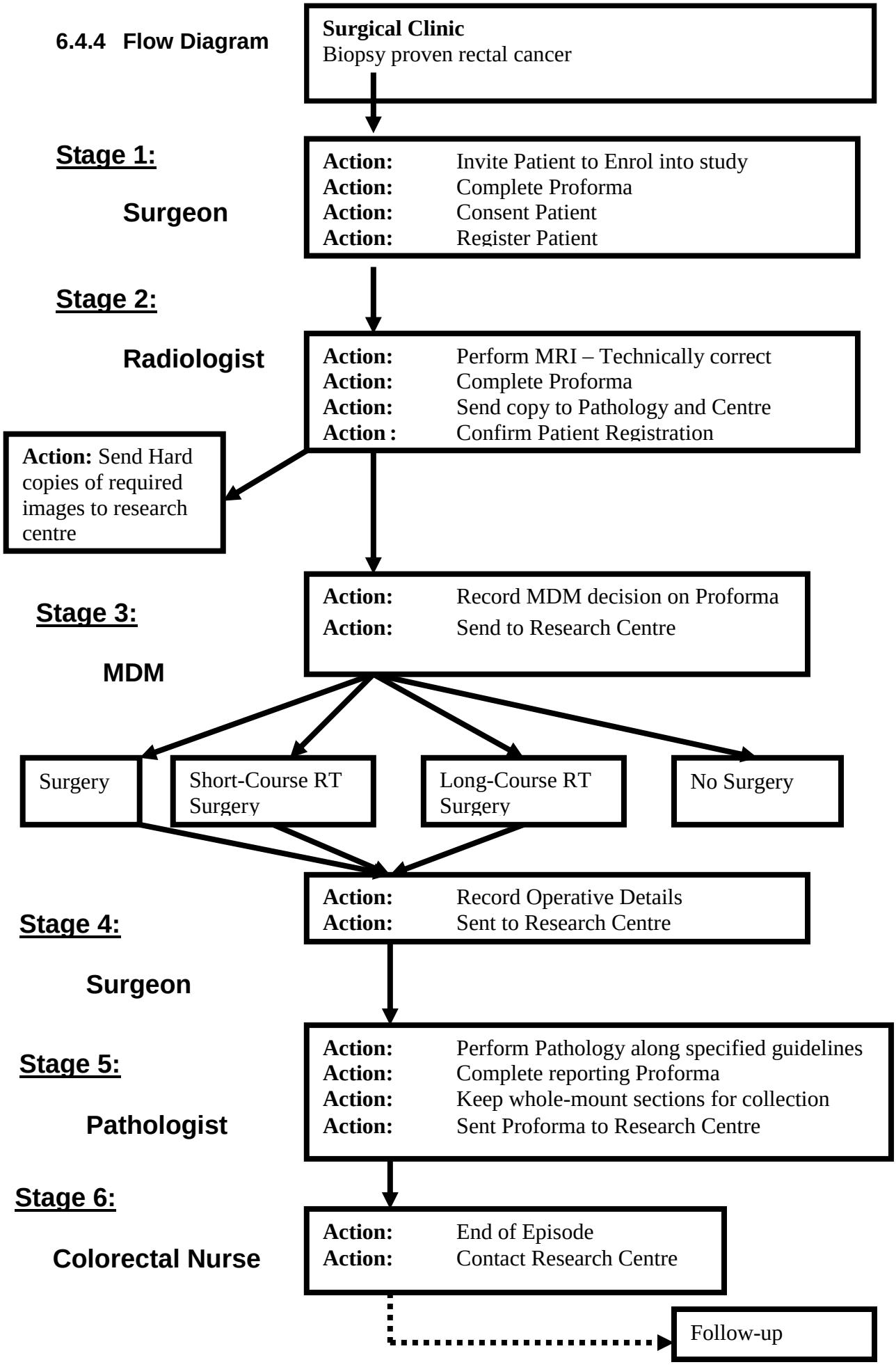
The study will be coordinated via a Surgical Research Fellow, based at The Pelican Centre, Basingstoke, England.

At inception of the study a central-based Steering Group was founded. As we wrote the protocol,this will comprise an independent Chairman, the Research Fellow, the Pelican Centre Director, two Surgeons, Pathologist, Oncologist, Statistician, Research Supervising Radiologist and a second Radiologist. All study issues will be focused at this group and management decisions made by them.

Any major change in study direction will be addressed to all members of the study group. It is envisaged that the Steering Group would meet at intervals no greater than three months. The whole study group will meet at the inception of the study and at finality (one year). Sub-speciality meetings will be arranged for training and quality control (Radiology – Epsom, November and Pathology – Basingstoke, December).

(The members of the Steering Group are given in Appendix 2).

### 6.4.4 Flow Diagram



# 7 MEASUREMENTS AND ASSESSMENTS

## 7.1 Safety Measurements.

### 7.1.1 Patient monitoring.

Patients will be monitored as per normal practise leading up to and after surgery. Patients will also be provided with a research booklet detailing the study that is being performed. Any parallel studies that are on going in the individual units will have their own monitoring in those centres that form part of these separate studies. These studies and their outcomes will not affect this study (For example the CRO-7 and EXPERT Trials).

Full information about the study, MRI and rectal cancer will be provided.

### 7.1.2 Clinical Laboratory Tests.

No laboratory tests will be required for the study.

### 7.1.3 Magnetic Resonance Imaging (MRI)

The MRI protocol will be standardised amongst all centres for data collection. All forms will be submitted centrally via facsimile. (An example of the MRI data collection form can be seen in Appendix 3).

MRI inclusion and exclusion criteria will be standardised in line with current safety recommendation for MRI.

In those centres taking part in the study, MRI is used as routine clinical practice and no additional imaging will be required.

## 7.2 Study Centres and Duration of Study.

Enrolment to the study will be conducted over a total period of up to fifteen months, and is planned to commence in early 2002. All centres will agree to approach all patients (NHS and Private) diagnosed with primary rectal cancer and consent to submit information to the database. This is to allow a full and accurate assessment of the management of rectal cancer and the role of MRI.

It is envisaged that approximately 460 patients will need to be recruited (refer to Statistics – Section 15).

## 7.3 Study Procedures.

Patients fulfilling the entry criteria will be enrolled into the study after they have signed the informed consent form. Upon enrolment, but prior to initiation of the surgical procedure, patients will undergo the required investigation - MRI.

Following surgery patients will be approached to be followed up for a period of five years to allow a prospective rectal cancer registry to be developed for further research to be performed to allow development of a Pre-Operative MRI Scoring System (P.O.M.S.S.).

## 7.4 Patient Registration

Patients will be entered into the trial by a telephone call to the Trial Centre, based at the Pelican Centre (01256 314547). Details will be left on an answer-phone. Informed consent for entry into the study must be obtained prior to registration.

The following information will be required at the time of registration:

Name of Surgeon
Submitting Hospital
Name of Patient
Patient's date of birth
Patient's address

This will allow registration of patients at any time. The trial office will then contact the surgeon concerned to allow full entry of the patient to the trial. The answer-phone message will also remind the surgeon to consent the patient for the study.

Once eligibility has been confirmed and the necessary details obtained the patient will be considered fully registered and the Oncological, Radiological and Pathological Departments accessed for further information.

As a further check that all cases have been included and to allow accurate assessment of all rectal cancers, the Radiologist will be asked to ring in with details of any patient who has undergone MRI at the time of reporting.

The central role of the Clinical Nurse Specialist as a local co-ordinator of the trial data and investigations is important for success of the trial and a separate pre-trial meeting will be arranged for them.

# 8 PATIENT POPULATION

All patients recently diagnosed with a primary rectal cancer during the study period will be approached to be included in the study.

## 8.1 General Inclusion criteria.

1. Willing, able to and having freely given written consent to participate in the study and abide by its requirements.
2. Adults age 18 or over – male or female
3. Recently diagnosed with rectal cancer
4. No previous therapy for rectal cancer

## 8.2 General Exclusion criteria.

### 8.2.1 Pre-operative

Patients must be excluded if they meet any of the following criteria:

1. Current pregnancy, including ectopic pregnancy.
2. History of pelvic malignancy prior to study initiation (excluding carcinoma in-situ).
3. Previous pelvic radiotherapy.
4. Previous pelvic floor surgery for faecal incontinence or prolapse.
5. Previous rectal carcinoma

### 8.2.2 MRI Exclusion Criteria

Patients will be excluded from the study if they are unable to undergo MRI following current guidelines for MRI. These include:

1. Evidence of metal fragments within the eyes
2. Pregnancy
3. Implantable metal devise
4. Patients with pacemakers
5. Patients with artificial heart valves
6. Patients who have has surgery to the brain
7. Patients with cochlear implants

Some individuals may find the MRI a distressing experience due to claustrophobia or cardio-respiratory compromise. Whilst we aim to exclude only the above there will be individuals who cannot tolerate the imaging. It is expected that they will form less than 5% of the total.

## 8.3 Drop out or Withdrawal.

The reason for withdrawal and the date of withdrawal must be documented in the case record form. This allows for an accurate assessment of patients with rectal cancer and current therapy.

## 8.4 Data Collection

All data will be collected, monitored and computerized centrally at The Pelican Cancer Trust Research Office. All patients who are approached to enter the trial should be logged including those who refuse to give consent. Brief details of the reasons why patients are not included should be given.

**The aim is to have a minimum of 90% of all newly diagnosed rectal cancer patients registered for the trial.**

Individual data collection will be kept to a minimum with standardization of data collection forms.

The surgeon will need to consent the individual patients and to complete the entry checklist before submitting details to The Pelican Centre. All other data will be collected separately.

# 9. RECTAL CANCER FACTORS.

## 9.1 Inclusion Criteria

All patients newly diagnosed with rectal cancer are eligible to be entered into the trial. By including all cases this trial will represent an audit of current practice in the designated centres. To assess the feasibility and reproducibility of the MRI assessment as compared to the histopathology a TME specimen is necessary. .

## 9.2 Exclusion Criteria

Patients undergoing local excision of lesions within the rectum will be excluded from the final analysis. Any patient receiving a palliative bypass will also be excluded, as no pathological specimen will be available. However, data on these patients will be kept for the audit of current practice.

## 9.3 Short-Course Radiotherapy (SRT).

It is recommended that all patients who receive SRT should undergo surgical excision within five days of the completion within this study. It is not anticipated that the use of short-course radiotherapy will alter the histopathological assessment for the above reasons.

## 9.4 Long-Course Radiotherapy (LRT).

In those patients in whom the initial assessment suggests advanced local disease with fixation or clear breach of the mesorectal fascia on MRI, then local policy may suggest long-course radiotherapy. In these patients repeat MRI assessment will be useful to compare to the initial scans and the histological specimen to assess for tumour down-staging. This will provide a further sub-group for analysis.

## 9.5 Combination Chemo-Radiotherapy (CRT).

Local policy may dictate the use of combination therapy and the addition of chemotherapy will need to be assessed with repeat MRI assessment prior to surgery. Again these patients will provide a further sub-group for analysis.

## 9.6 Local Policy.

Prior to commencement of the study each centre will specify the members of the multidisciplinary team involved in the study and will clarify their current policy regarding pre-operative chemo- radiotherapy and radiotherapy, including regimes used and dosage schedules.

If an individual centre's policy is to irradiate the majority of patients with concurrent long course chemo-radiotherapy, irrespective of the clinical findings, then they will be excluded from the study, as the pathological correlation will be altered.

(See Appendix 4 – Local Policy Form)

# 10. SURGICAL FACTORS

## 10.1 Inclusion Criteria

The following criteria need to be met by individual surgeons

1. All surgical units involved in the study must agree to include details upon all patients (NHS and Private) with rectal cancer.
2. The technique of Total Mesorectal Excision must be employed for low rectal cancers and partial mesorectal excision with division of the mesorectum 50mm below the tumour for upper rectal cancers.
3. The surgeon must obtain informed consent from the patient having fully explained the nature of the trial and current practice.
4. The surgeon must be part of a multi-disciplinary team involved in the management of rectal cancer and the patient discussed at the MDM prior to commencement of therapy.
5. Histological proven adenocarcinoma of the rectum within 15cm of the anal verge when measured using a rigid sigmoidoscope with the patient in the left lateral position.

## 10.2 Diagnosis

At diagnosis in the outpatient clinic the site of the tumour must be clearly documented. The surgeon at the initial assessment must note local factors about the tumour and its relationship to the pelvic floor. These factors will form the details necessary to register the patient (Appendix 5 – Patient Registration Form).

## 10.3 Operative Surgery

At the end of the operation the surgeon will be asked factors related to the resection of the rectal cancer and the operation performed. This will include on-table assessment of tumour height, the relationship to the pelvic floor and the peritoneal reflection, local clearance – both laterally and distally and evidence of local or distant disease at the time of surgery.

The surgeon will also be asked to classify the resection specimen as

TME performed, mesorectal fascia intact [ ]

TME performed, mesorectal fascia breached [ ]

Surgically obvious margin involvement [ ]

(An example of the Operative Proforma is shown in Appendix 7).

# 11. MRI PROTOCOL

## 11.1 MRI Assessment

The definition of a technically valid MRI examination must include the following:-

1. Demonstration of the tumour in the correct plane.
2. High resolution of images
3. Satisfactory image quality showing the tumour, the mesorectal fascia, the outer muscle coat and coverage of tumour and deposits
4. The pelvic floor and its relationship to the tumour.

(The recommended MRI Technique is given in Appendix 8).

## 11.2 Data Collection

Prior to commencement of the study a Radiology Trial Day will be arranged (7th November 2001). This is to test the ease of use of study proformas and to assess inter- and intra-observer variation in reporting MRI images.

To allow for accuracy of reporting and correlation with the histopathological specimen a standardised reporting form has been designed (See Appendix 3a).

To allow for accurate histological assessment of the specimen the Pathologist will be guided by an MRI Proforma identifying areas of interest on the scans (See Appendix 3b).

The Radiologist will also have a checklist of suspected features for the Pathologist (See Appendix 3c)

All MRI films in patients in this study will be doubly reported by the Radiology Supervisor (Dr Gina Brown). Hard copies of all films will be saved in the initial period although improved electronic data collection may allow the transmission of images.

(The collection and transfer of images is the subject of Appendix 8).

## 11.3 Standardised Terminology in MRI Reporting

### 11.3.1 Extra-mural depth of invasion

For each patient the maximum depth of penetration beyond the outer longitudinal muscle layer is measured on the workstation using electronic callipers. Measurement of the maximum extramural depth from outer muscle layer to outer edge of tumour is recorded.

### 11.3.2 Lymph node involvement

A lymph node is defined as involved by tumour if it returned either a mixed signal intensity or had irregular or ill-defined borders.

### 11.3.3 Extra-mural vascular invasion

This is defined as demonstration of tumour extension along a vessel resulting in a serpiginous extension of tumour signal within a vascular structure (a vessel was defined as a tubular structure containing signal void on T2 weighted images with continuity on adjacent slices).

### 11.3.4 Circumferential Resection Margin Involvement (CRM +ve)

Involvement of the mesorectal fascia (the potential circumferential margin) by tumour is defined as tumour, tumour deposit or lymph node abutting or extending through the mesorectal fascia or extending to $\leq$ 1mm of the mesorectal fascia.

### 11.3.5 Perforation of the peritoneal reflection by tumour

This is defined as nodular extension of tumour beyond the peritoneal reflection.

### 11.3.6 Distance to the Anal Sphincter

In low rectal cancers the distance from the lower margin of the tumour to the upper border of the external sphincter should be recorded together with the distance from the lowest part of the internal sphincter.

### 11.3.7 MRI Pelvimetry and assessment of operability

For low rectal cancers we intend to measure the anterior-posterior distances of the mesorectum and rectal muscle tube as well as the corresponding lateral dimensions at the mid-acetabular level.

The minimum inter-ischial tuberosity distance and the minimum pubo-coccygeal distance will be measured.

## 11.4 Patients Receiving Long-Course Radiotherapy (LRT)

Patients will have been imaged prior to the MDT Meeting and then allocated to LRT on the basis of their advanced disease. Following radiotherapy the patients need to be re-imaged to assess response to the therapy. This should be performed following completion of LRT.

If there is a gap to surgery (> 6 weeks) a further set of images (High Resolution Axials of the tumour) may be useful 7-14 days prior to surgery.

## 11.5 Patients Receiving Chemo-Radiotherapy (CRT)

Patients will have been imaged prior to the MDT Meeting and then allocated to CRT on the basis of their advanced disease. Following chemo-radiotherapy the patients need to be re-imaged to assess response to the therapy. This should be performed following completion of LRT. If there is a gap to surgery (> 6 weeks) a further set of images (High Resolution Axials of the tumour) may be useful 7-14 days prior to surgery.

# 12. HISTOPATHOLOGICAL FACTORS

## 12.1 Specimen Receipt

Ideally specimens should be received fresh and the front and back of the specimen digitally photographed prior to opening. The specimen should be scored for the audit of surgical practice and should be reported as:

| | |
|---|---|
| Grade 1 | Good: Intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect greater than 5mm. No coning on the specimen. Smooth CRM on slicing. |
| Grade 2 | Moderate: Moderate bulk to mesorectum but irregularity of the mesorectal surface. Moderate coning of the specimen towards the distal margin. At no site is the muscularis propria visible with the exception of the area of insertion of levator muscles. Moderate irregularity of the CRM. |
| Grade 3 | Poor: Little bulk to mesorectum with defects down onto muscularis and/or very irregular CRM. Specimen unacceptable for MRI equivalence |

The upper and lower borders of the tumour should be identified and proximal and distal resection margin distances recorded on the fresh specimen. This will allow the study of the quality of the surgery around the tumour and whether surgical deficiencies are present below the tumour, at the tumour or above.

## 12.2 Specimen Fixation

The specimen should be opened to within 2cm of the upper border of the tumour. This will facilitate entry of the formalin to fix the specimen and allow access should fresh tissue sampling be performed. The open specimen should then be pinned to a corkboard and fixed for 48-72 hours. After fixation the specimen should be removed from the board and the non-peritonealised surfaces painted with ink by the method used locally. If images of the whole fresh specimen were not obtained then these should now be recorded digitally.

## 12.3 Specimen Assessment

### 12.3.1 The ‘Cut-up’ Technique

At 'cut-up' a description of the relationship of the tumour to the rectum, the peritoneal reflection and the resection margin are noted. The specimen should be scored to assess the quality of the mesorectum as above and photographed as per protocol above.

The area of the tumour that has been left intact is the sectioned transversely as thinly as possible (ideally 3mm sections). These sections are then laid out consecutively and further digital imaging performed of all sections

macroscopically. It is critical to the study that sections of the tumour are taken perpendicular to the rectum. This is to allow direct comparison with the MRI image.

If available, whole-mount blocks of the relevant sections should be made although ¼ blocks are acceptable if whole-mount sectioning is unavailable.

To aid identification of the areas of interest from the MRI the pathologist will receive a diagram of the MRI sections from the radiologist.

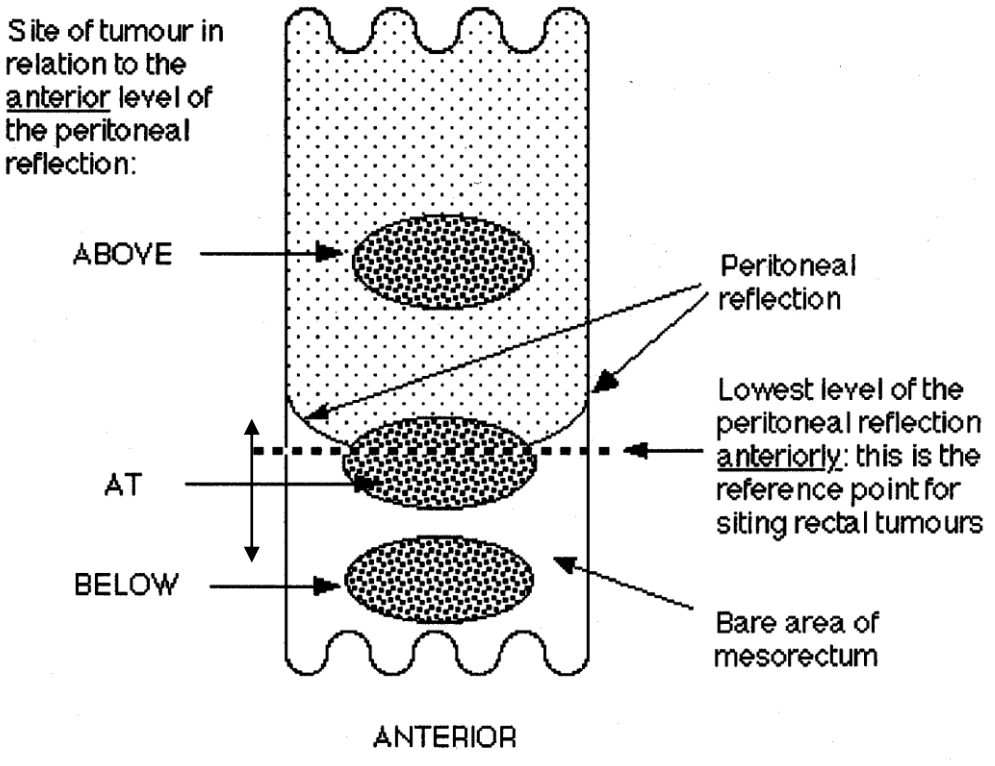
### 12.3.2 Position of the tumour

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

### 12.3.3 Relationship to the peritoneal reflection

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

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



### 12.3.4 Relationship to the CRM

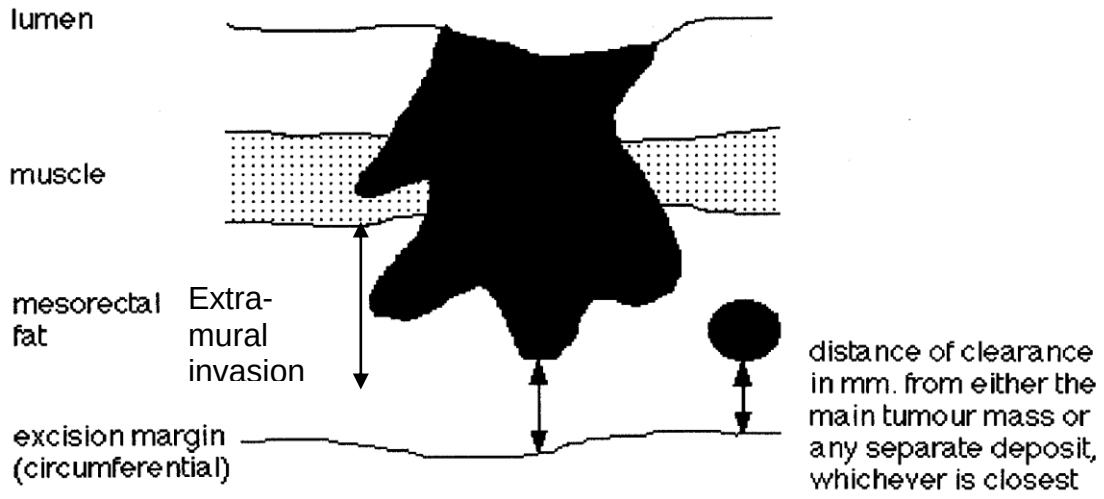
Anteriorly the rectum is covered by peritoneum and only the area below the peritoneal reflection is at risk of circumferential margin involvement. Posteriorly this area, and the area above it, a triangular shaped bare area running up to the start of the sigmoid mesocolon, is at risk not only from direct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

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

A whole-mount section of the piece of tissue with the suspected closest resection margin is then made. The minimum distance between the tumour and the circumferential margin (i.e. the serosal surface of the mesorectum), measured in millimetres using the Vernier scale on the microscope is then recorded from the histological slides. If this is < 1mm then the CRM should be regarded as involved in the assessment of completeness of resection. Such involvement may be by direct continuity with the main tumour, by tumour in veins, lymphatics or lymph nodes, or by tumour deposits discontinuous from the main tumour (See Figure in 12.3.5). A digital image of this section should be recorded.

### 12.3.5. Relationship to Extra-Mural Invasion

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



### 12.3.6 Lymph nodes

All lymph nodes found in the specimen should be sampled and counted, regardless of their site and size. A median number of 12 nodes need to be identified in all specimens.

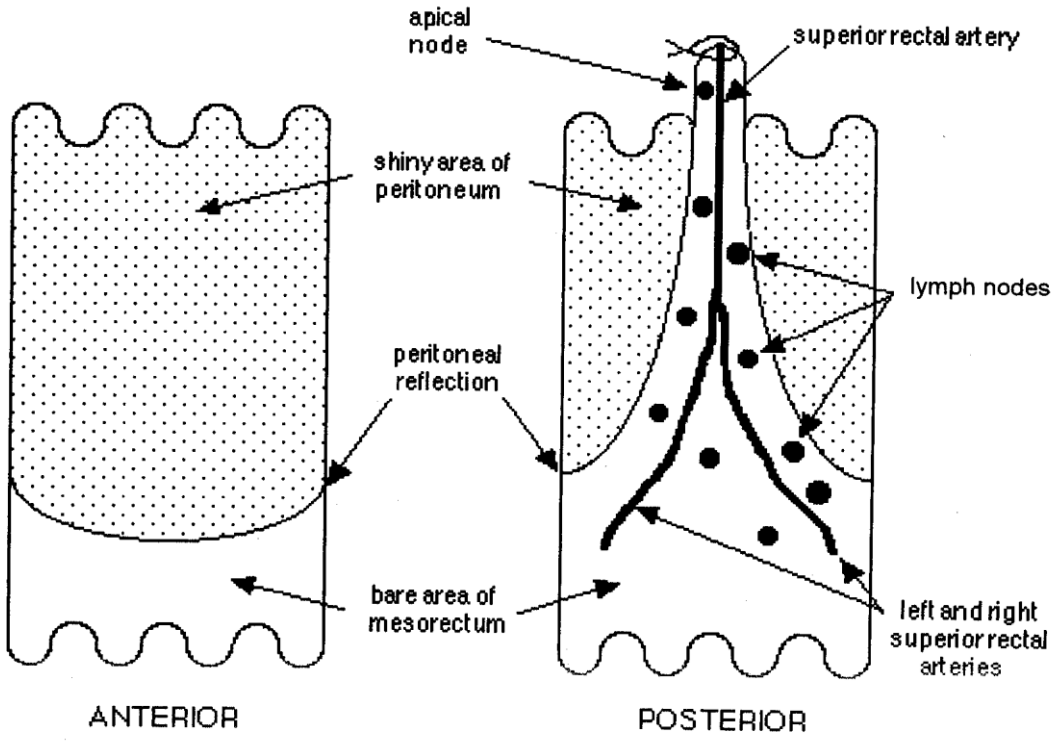
The number of positive lymph nodes must be equal to or less than the number of lymph nodes sampled.

Extramural tumour deposits measuring ≥ 3 mm are counted as involved lymph nodes even if no residual lymph node structure can be identified.

Smaller deposits are regarded as apparent discontinuous extensions of the main tumour.

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

For Dukes' staging the pathologist will need to identify separately the apical node closest to the main vascular tie.




### 12.3.7 Extramural Vascular Invasion

This is recorded when tumour is present within an extramural endothelium-lined space that is either surrounded by a rim of muscle or contains red-blood cells. Of special interest are the sites of extra-mural venous invasion that involve vessels >3mm in diameter. There position should be recorded on the reporting proforma.

### 12.3.8 Distance to the distal resection margin

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

### 12.3.9 Relationship to the Dentate Line

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

If the tumour has perforated into the peritoneal cavity or is clearly present beyond the edge of the mesorectal fascia then these cases should be regarded as pT4 in the TNM staging system.

## 12.4 Post-LRT and CRT Specimens

These should be assessed using the standard method. However, these specimens will not be included in the final assessment. These will be used to assess tumour response to therapy and correlation between repeat MRIs following completion of therapy but prior to surgery. Assessment of tumour response and fibrosis will prove helpful in the review of the MRI staging.

## 12.5 Assessment of Abdomino-perineal Excision

After standard tumour assessment with additional information on the relationship of the tumour to the dentate line, and therefore the sphincters, further information can be gained in the assessment of the capabilities of the MRI.

Photographic evidence of the specimen can be used to assess the development of a ‘waist’ on the specimen following TME and then anal excision. Again the value of MRI on assessment in relation to the sphincters and the separate discussion of the role of an APE can be discussed.

## 12.6 Retention of Tissue

All patients as part of the consent process will be asked to donate a piece of their cancer and normal tissue for tissue-based cancer research. There will be an opt-out clause to the consent form.

(This is further discussed in Section 19)

# 13. ONCOLOGICAL FACTORS

## 13.1 Individual Units – Neo-adjuvant Radiotherapy

Individual policies for the use of neo-adjuvant therapy must be defined prior to the initiation of the study. For radiotherapy these must include;

1. Criteria for selection
2. Type of radiotherapy
3. Volume of the tumour/rectum to be irradiated
4. Dose and fractionation of the radiotherapy
5. Timing of the radiotherapy

## 13.2 Individual Units – Neo-adjuvant Chemotherapy

Individual policies for the use of neo-adjuvant therapy must be defined prior to the initiation of the study. For chemotherapy these must include:

1. Criteria for selection
2. The regimes used

Some units will use a combination of chemo-radiotherapy prior to surgery and these combined protocols need to be included.

## 13.3 Post-operative Radiotherapy

It is not envisaged that post-operative radiotherapy will be used in the context of this trial, unless tumour excision has not been performed along the lines of TME or there was evidence of local tumour at surgery that had not been pre-operatively imaged. This may be the case in emergency surgery.

## 13.4 Post-operative chemotherapy

This trial is not designed to test the effect of systemic chemotherapy, but to follow local treatment protocols. Therefore individual units may administer chemotherapy either within an appropriate local trial or using a standard regime according to local policy.

Patients receiving adjuvant chemotherapy only should commence once post-operative recovery is sufficient, optimally 4-6 weeks after operation.

# 14. FOLLOW-UP OF PATIENTS

For this initial part of the study no patient follow-up is required. However, to allow further development and research in the field of MRI staging of rectal cancer a database for follow-up will be created. This is to assess the feasibility of a Pre-Operative MRI-based Prognostic Staging System (P.O.M.S.S.) for rectal cancer.

**There is an opt-out clause in the Investigator Agreement for Units not wishing to join any Follow-Up Studies.**

## 14.1 Current Follow-Up.

Each unit will be asked to submit their current practice guidelines regarding the intervals for follow-up, length of follow-up, follow-up investigations and policy for the diagnosis and management of local recurrence.

## 14.2 Suggested Follow-Up

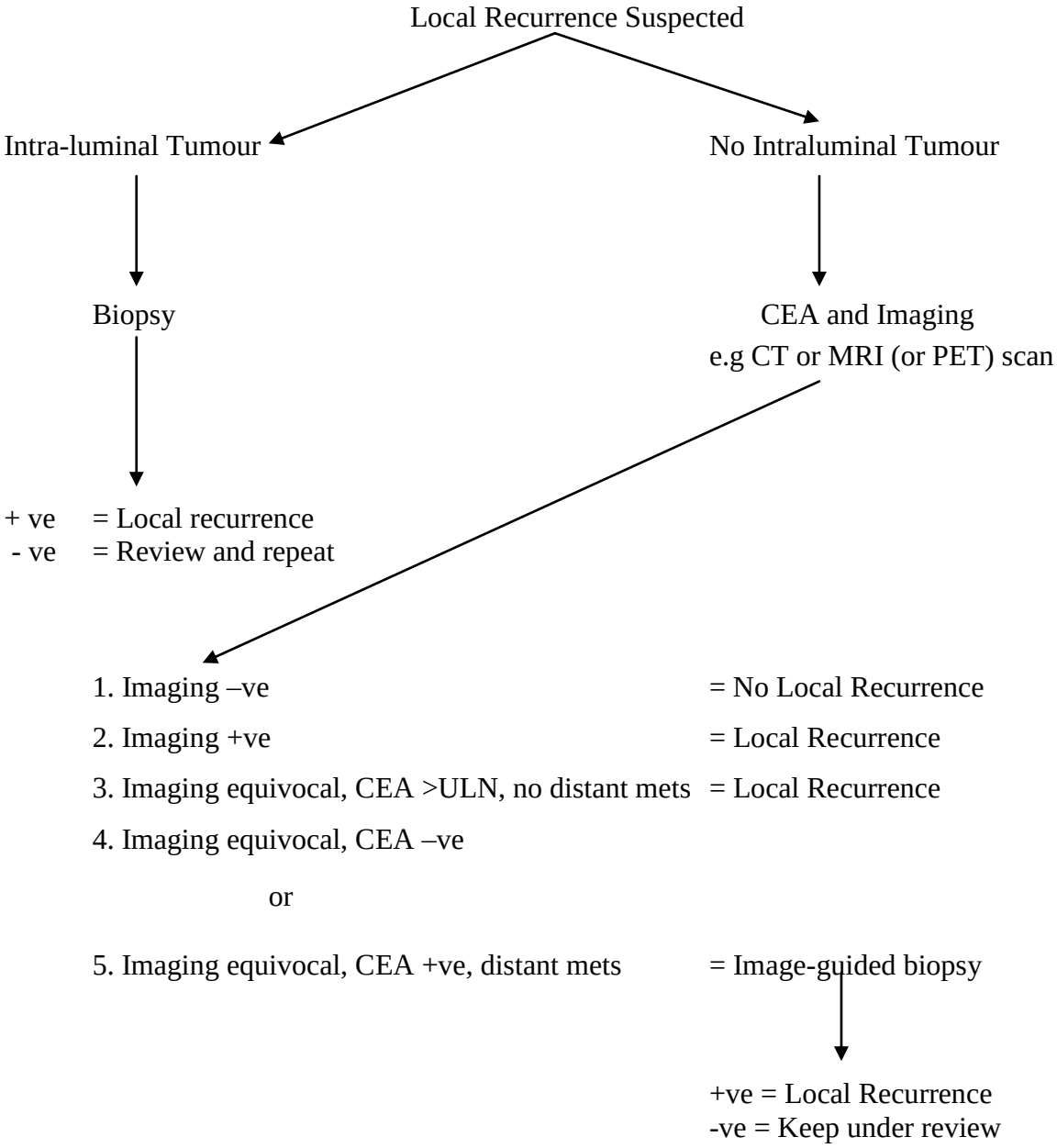
The suggested follow-up protocol is as follows:

| | |
|---|---|
| 4 Weeks | To assess immediate morbidity and mortality |
| 3 Months | Follow-up and rigid sigmoidoscopy<br>Baseline CT of Pelvis |
| 6 Months | Follow-up and rigid sigmoidoscopy |
| 9 Months | Follow-up and rigid sigmoidoscopy |
| 12 Months | USS of liver, CEA, and Colonoscopy<br>CT of Pelvis |
| 18 Months | Follow-up and rigid sigmoidoscopy |
| 24 Months | USS of liver, CEA, and rigid sigmoidoscopy<br>CT of Pelvis |
| 30Months | Follow-up and rigid sigmoidoscopy |
| 36 Months | USS of liver, CEA, and rigid sigmoidoscopy |
| 48 Months | Follow-up and rigid sigmoidoscopy |
| 60 Months | Follow-up and rigid sigmoidoscopy |

**Endpoints are the development of recurrence (local or distant).**

## If distant recurrence continued re-assessment for local disease.

### 6.1 Definition of Local Recurrence




(CEA +ve defined as > upper limit of local normal value)

# 15 STATISTICAL ANALYSIS

## 15.1 Sample size for demonstrating equivalence

The single most important factor in the equivalence study of MRI and the histopathological assessment is the relationship of the extramural depth and specimen margin to the mesorectal fascia on MRI and on specimen analysis.

These become the primary end-points in the study. The following calculations are based on good TME surgery, standardised MRI radiological reporting and standardised histopathology reporting. Therefore the primary endpoints are:

1. Equivalence between the pathology measurement and the MRI measurement of the extra mural depth of the tumour (the difference should equal zero +/- 0.5mm).

2. The rate of CRM –ve after MRI selection will be greater than 90% and in the region of 95%.

## 15.2 Primary Endpoint 1

When demonstrating equivalence it is important to establish clearly the principals underlying the final analysis prior to starting the trial. A number of quantities should be defined.

1. Alpha ($\alpha$): This is the type I error, in equivalence studies this represents the probability of missing equivalence. Conventionally this quantity is set to 0.05 but with equivalence studies this may be larger.

2. Beta ($\beta$): This is the type II error and represents the probability of falsely claiming equivalence. This quantity should be small in equivalence studies. Power = $100(1 - \beta)$.

3. Eta ($\varepsilon$): is the maximum allowable difference to be detected. If the $100(1- \alpha)$ confidence interval includes values beyond this value then the claim for equivalence would be rejected.

The optimum design would be to set $\beta = \alpha/2$ thus excluding certain inconclusive scenarios in the final analysis and definite conclusions may be reached regarding equivalence and efficacy.

In this study we will examine the difference between the histopathology measurements and the MRI measurements. If there is no difference then this will equal zero. A two sided test should be used as we wish to test for differences both greater and less than zero.

The following assumptions are used in this study:-

1. The standard deviation of the difference between histopathology measurements and MRI measurements is 1.5 mm.
2. The maximum allowable difference in the measurements ($\varepsilon$) = 0.5 mm
3. $\alpha = 0.05$
4. $\beta = \alpha / 2 = 0.025$ therefore power = 97.5%
5. Two sided tests used.
6. In the final analysis the 95% confidence interval of the difference between histopathology measurements and MRI measurements will lie exclusively within the range ($-\varepsilon$, $\varepsilon$) i.e. (-0.5mm to 0.5mm)

Therefore the total sample size required will be 277 patients (1). However, 300 patients with T1 – T3 tumours will be recruited to allow for data losses.

However, if we assume 10% will have advanced disease (T4), 10% will present with widespread disease and 15% will undergo Abdomino-Perineal Excision, the sample size is larger.

### 15.2.1 Interim analysis for the first primary endpoint.

An interim analysis using an $\varepsilon$ of 1.0mm will be tested based on the first 100 patients recruited. This will establish whether the trial is unlikely to achieve its' primary equivalence endpoint.

## 15.3 Secondary Endpoints

These will be divided in sub-sections based on speciality

### 15.3.1 Surgical

See Section 4.3

### 15.3.2 Radiological

It is hoped that this study will demonstrate that with the use of MRI to aid decisions about preoperative treatment the rate of CRM –ve resections will be in the region of 95%, but we would like to rule out a lower limit of 90%.

The study will use a Simon single stage design (2) to rule out a CRM –ve rate of less than 90% with an estimated true rate of 95%. With a power of 95% and a 1-sided Alpha of 0.05 the study would require that more than 277/298 patients will be CRM negative to demonstrate that a rate of less than 90% could be ruled out.

See Section 4.3 for further secondary endpoints.

### 15.3.3 Pathological

See Section 4.3

### 15.3.4 Oncological

See Section 4.3

## 15.4 References

1. Machin D, Campbell MJ, Fayers PM, Pinol APY. Sample Size Tables for Clinical Studies, 2nd ed. Oxford: Blackwell Science, 1997.

2. A'Hern RP. Sample size tables for exact single-stage phase II designs. *Stat.Med.* 2001;20:859-66.

# 16 DATA MANAGEMENT

## 16.1 Data Collection Forms

All data will be collected in booklets produced through the Pelican Centre. They will be individually numbered for the unit, the surgeon and the patient. Each will have the facility to tear out and then fax the relevant page. Consent for the study will remain in the patients' hospital notes. All forms will be standardised A4.

## 16.2 Data Downloading

### 16.2.1 Written Data

Data will be transferred from the hard copy to the data management system at the Research Office. All hard copies will be retained and stored securely.

### 16.2.2 MRI Image Data

Where possible the images will be stored both as a hard copy and as a .tif or jpeg file on a CD. Further work in collaboration with the MRI Operating Companies (Lodestone or Alliance (PFI) or the NHS) and Siemens Medical Systems will allow direct downloading of the images to a PC. This may be by the use of systems such as E-File. Again all CD stored information will be held separately and stored securely.

## 16.3 Database System

The data storage tool will be the Royal Marsden Data Management System. This system has been used and modified over the last 15 years and has a proven 'track record.' It can be accessed via the NHS Intranet and data exported as an Excel file to other sites within the intranet. All centres will be encouraged to use the NHS Intranet to transfer data.

## 16.4 Data Interpretation

Analysis will be performed using SPSS for windows. Again data can be easily transferred from the RMH system for data analysis. This will be performed with the help of the Study Statistician.

## 16.6 Missing Data Collection

Missing data will be identified on a weekly basis (Monday am) and then an e-mail will be sent to the relevant Surgeon/Radiologist/Pathologist/Colorectal Nurse via the NHS Intranet. Further contact will be made by telephone or by direct contact at the centre.

## 16.7 Follow-up Data Collection

To allow for the collection of follow-up data the data collection system will be adapted to generate the follow-up intervals for the patients. In those centres

wishing to take part in follow-up studies all data must be collected prospectively using agreed local follow-up protocols.

Direct entry of data can then be performed.

To allow for patient movement the NHS Statistical Agency has been approached to generate data on patient deaths. Every three months all patients admitted to the trial will be searched on the death register and data made available.

# 17. REGULATORY AND ETHICAL REQUIREMENTS.

## 17.1 Ethics Committee Submissions and Approval.

Central ethical approval will be applied for and registered with COREC and envelope approval will be sought. Local ethical committees will be approached with the trial protocol following MREC approval.

(For European centres local approval must be sought and local ethical approval will need to be clarified)

## 17.2 Written Informed Consent.

The study, and the risks and benefits of participating in the study, will be explained to the patient in understandable, non-medical language by the investigators. The patient will be given time to read the Patient Informed Consent Form (an example is given as Appendix 1) and all questions raised by the patient must be answered. The patient and the investigator or designees will sign the informed consent form, and a copy will be placed in the patient's study notes. The original will be kept with the patient's medical notes.

## 17.3 Patient Confidentiality.

Patients will be identified during the course of the study by their initials and study number only. All study personnel and the Regulatory Authority representatives will maintain patient confidentiality at all times.

## 17.4 Investigator Confidentiality

All investigators – Surgeons, Radiologists and Pathologists will be issued with a randomly generated code number that will be used for their own identification during the study. Each individual will be given access to their own data during the study, but individual clinicians will not be directly compared.

## 17.5 Protocol Amendments.

Any change in study design must be agreed upon by the all members of the steering committee and major protocol amendments (those altering the nature of the study) by all collaborators. The amendments must be submitted to the steering committee by the investigator and where appropriate the amended patient informed consent form will accompany this submission. Changes will be made to the case record forms if appropriate.

# 18. REPORTING AND MONITORING CONSIDERATIONS.

## 18.1 Quality Control

An independent Data Monitoring Committee will be formed to allow outside assessment of the quality of the data and the trial aims. It is proposed that after the trial is commenced and when 100 patients have been recruited this body would meet. They will be tasked with the following questions:

1. Is the quality of the data of the standard necessary for the trial to proceed?
2. Are all the centers submitting data correctly
3. Is reporting of the data accurate
4. Are the objectives of the trial being attained
5. Does the interim analysis support the trial hypothesis

(The members of this committee are given in Appendix 11).

## 18.2 Device Accountability.

All patient data will be stored on a central PC held at the Pelican Centre. This will be password protected and only contain the patients study number and hospital number. Individual names and addresses will not be used.

## 18.3 Case Report Forms and Study Documentation.

All patient data forms and hard copies of all MRIs will be held centrally. Digital images taken will only be identified by the patients study number and hospital number. Individual names and addresses will not be used.

## 18.4 Storage of Study Documentation.

All study related material and patient datasheets would be kept in a secure area. MRI images will also be kept secure.

## 18.5 Medical Records and Source Documents.

An approach will be made to local ethical committees after COREC application. Follow-up of patient will require review of medical records and will be performed by individual units and submitted centrally or by the Pelican Research Fellow

## 18.6 Data Ownership, Publication and Reporting.

The Principal Investigator (Research Fellow) shall be free to publish the results of the study provided that the manuscript or abstract proposed to be published shall be submitted to the collaborative group **at least thirty (30) days prior to submission for publication** for review and comment.

**All results must be treated as strictly confidential until they are published.**

## 18.7 CONSORT Statement

Although this study is not a randomized clinical trial we aim to adhere to the CONSORT statement regarding items to include when reporting a trial. This goal is achieved through total transparency by the authors of any publications resulting from this study. Included in publications will be a flow diagram as outlined in the CONSORT Statement.

### 18.7.1 Reference

1. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel group randomized trials.

# 20. Personnel Responsibilities

The investigators and the sponsor undertake to conduct the study in conformity with the Declaration of Helsinki, the ICH European Good Clinical Practice recommendations and the law in force in the country concerned.

## 20.1 Investigator.

All participants in the study shall:

1. Adhere to the conduct of the study as described in this protocol.
2. Ensure the accuracy and legibility of the data collection forms.
3. Immediately report any serious adverse breaches in the study to the steering group.
4. Ensure appropriate data storage.
5. Maintain an accurate data accountability log.
6. Provide access at monitoring visits to the source documents, together with any other relevant medical information on the patients participating in the study.

## 20.2 Sponsorship

The funding for this trial has been achieved by education and research grants from Siemens Electronics and Medical Research, and The Wessex Cancer Trust. Neither body will have access to the data or external control on the organisation and management of the trial.

The Pelican Centre, a registered charity, as coordinating body shall:

1. Provide the research Fellow with all the necessary study documents and trial supplies prior to study initiation.

2. Provide the research Fellow with management support.

## 20.3 Early Termination

It is the intention that this study is carried through to its conclusion, but it is possible that for a number of reasons, the study (as any clinical study) may need to be stopped prior to its conclusion. In addition, the Steering Group reserves the right to terminate the agreement with the other collaborators.

1 Immediately upon substantial breach of the terms either of the agreement or of the conduct of the protocol

2 In the event that there are irregularities in the methodology by which the study is carried out and although capable of being rectified, are not rectified within 30 days of notice of this.

In the event of early termination, use of investigational materials will cease as soon as possible. All case record forms outstanding must be completed and returned to the Research Fellow with completed investigational materials inventory and records.

**Dear Patient.**

**Thank you for agreeing to take part in this study. Enclosed in this booklet is information regarding the study and forms for you to fill in to help with this medical research?**

# The M.E.R.C.U.R.Y. Project.

**Name** …….

**Address** …….
…….
…….
…….
…….

**Date of Birth** …….

**Your Consultant** …….

**Hospital** …….

**Dear Patient.**

**Enclosed within this booklet are some further questions and information for you to keep during your care. We will be keeping in touch with you to monitor your progress in the months and years following your operation.**

# The M.E.R.C.U.R.Y. Project

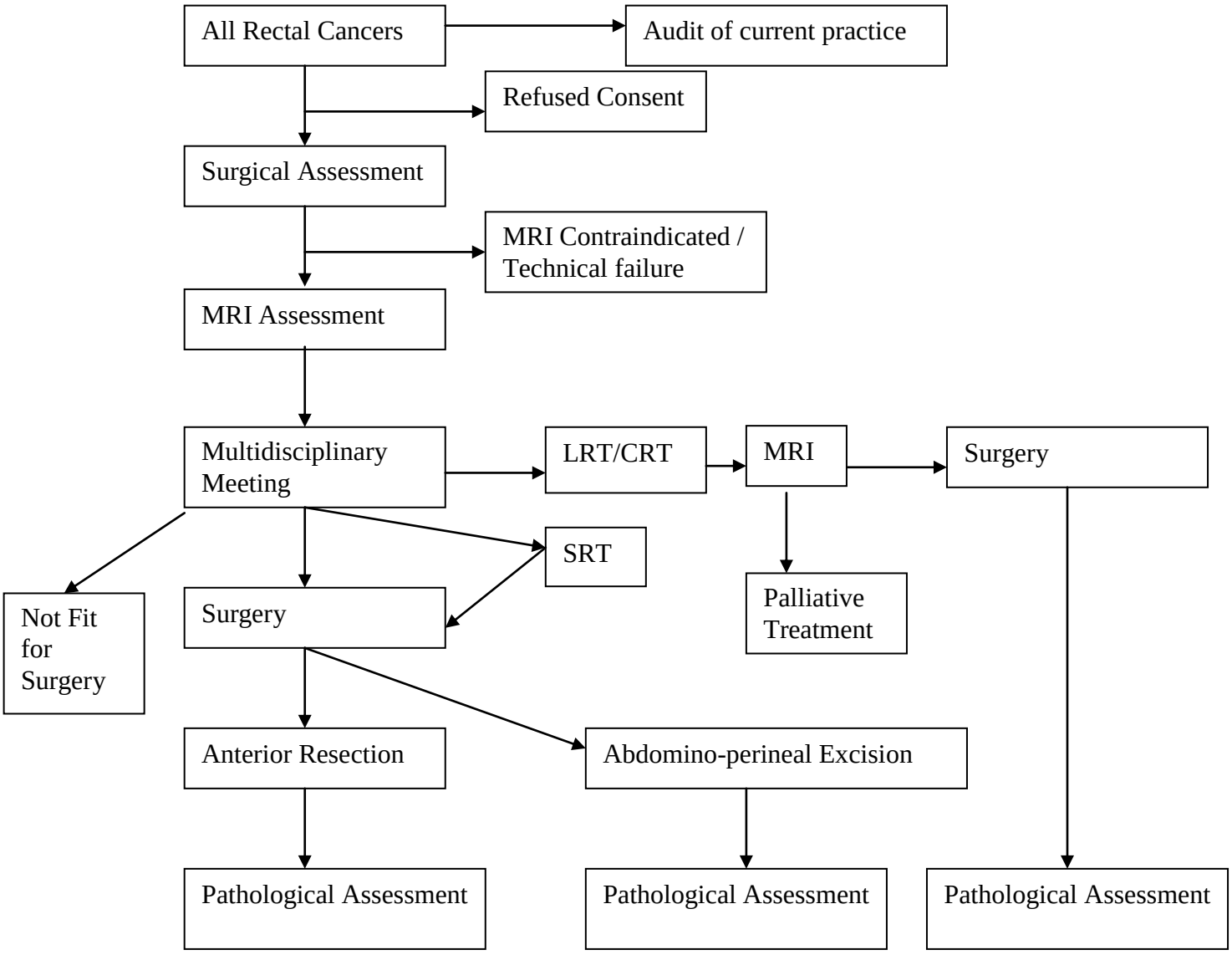
## Contents Of This Booklet:

| | | |
|---|---|---|
| Registration form for the study | To be signed by the Surgeon | [ ] |
| Consent for the study | To be signed by the patient | [ ] |
| Patient information sheet | To be given to the patient | [ ] |
| MRI information Booklet | To be given to the patient | [ ] |
| Pre-operative assessment form | Phone and register patient | [ ] |
| Pre-operative assessment form | Fax to Pelican Centre | [ ] |
| MRI Scan Form | Fax to Pelican Centre | [ ] |
| MRI Scan Pathologist Form | Send to Pathologist | [ ] |
| MRI Scan Checklist Form | | [ ] |
| Multi-Disciplinary Team Form | Fax to Pelican Centre | [ ] |
| Operation form | Fax to Pelican Centre | [ ] |
| Pathology Reporting Form | Fax to Pelican Centre | [ ] |
| Colorectal Nurse Form | Fax to Pelican Centre | [ ] |
| Study Contact Details | | [ ] |

Surgeon Radiologist Pathologist Nurse Patient

## OUTLINE OF THE STUDY

All adenocarcinomas of the rectum to be approached by each practicing surgeon

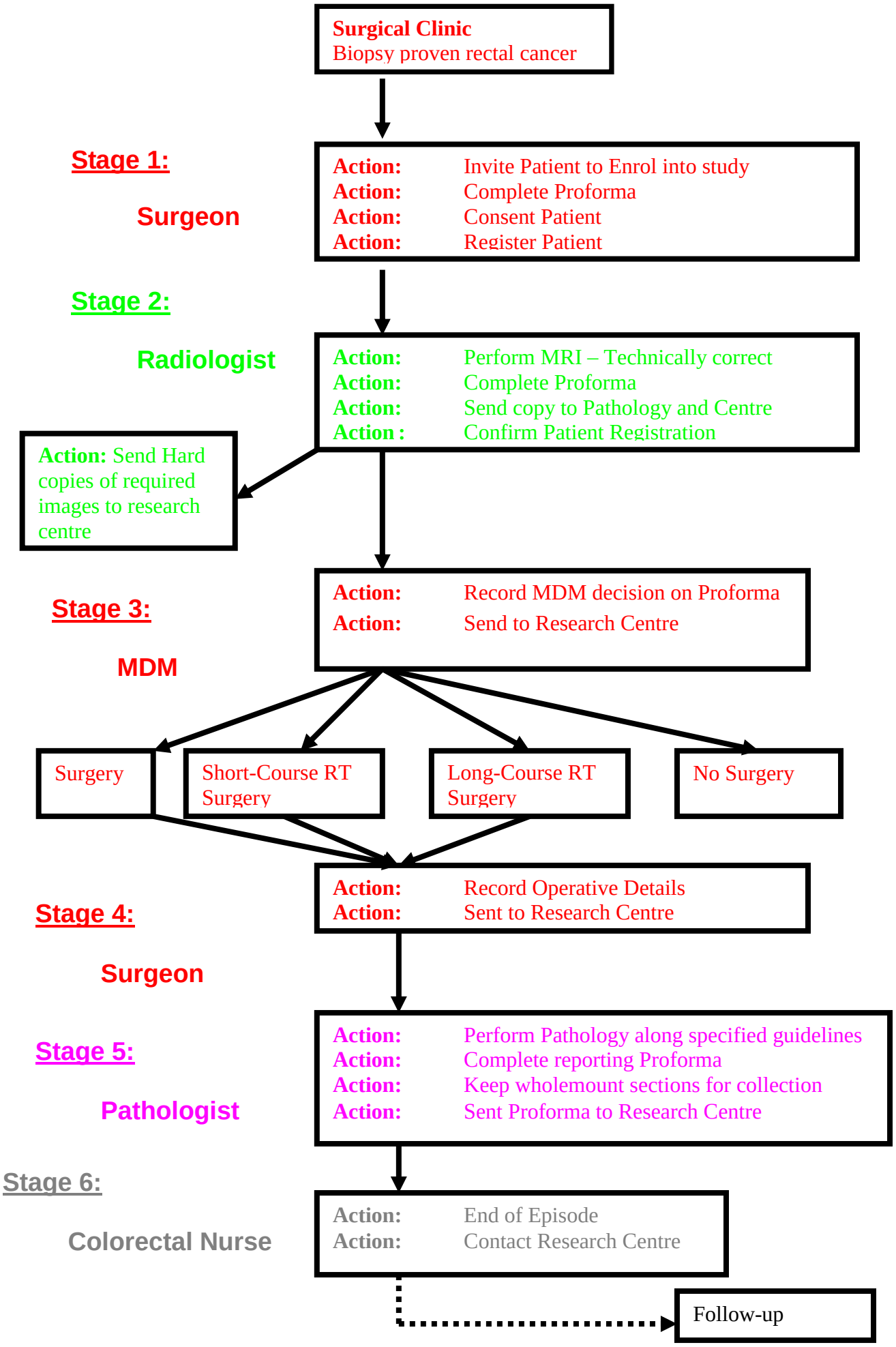



This group will form the basis of the MRI and histopathological equivalence study

This group will allow further MRI assessment of those tumours encroaching the anal canal

This group will allow assessment of the MRI appearance after neo-adjuvant therapy

**Primary endpoint: To Demonstrate Equivalence of MRI and Histopathological Assessment of Extramural Depth of Tumour Spread.**


Surgical Clinic
Biopsy proven rectal cancer
Stage 1:
Surgeon
Action: Invite Patient to Enrol into study
Action: Complete Proforma
Action: Consent Patient
Action: Register Patient
Stage 2:
Radiologist
Action: Perform MRI – Technically correct
Action: Complete Proforma
Action: Send copy to Pathology and Centre
Action : Confirm Patient Registration
Action: Send Hard copies of required images to research centre
Stage 3:
MDM
Action: Record MDM decision on Proforma
Action: Send to Research Centre
Surgery
Short-Course RT Surgery
Long-Course RT Surgery
No Surgery
Stage 4:
Surgeon
Action: Record Operative Details
Action: Sent to Research Centre
Stage 5:
Pathologist
Action: Perform Pathology along specified guidelines
Action: Complete reporting Proforma
Action: Keep wholemount sections for collection
Action: Sent Proforma to Research Centre
Stage 6:
Colorectal Nurse
Action: End of Episode
Action: Contact Research Centre
Follow-up

## Appendix 1: Consent Form and Patient Information Sheet

# The M.E.R.C.U.R.Y. Project.

**Dear Patient**

**Your surgeon is asking you to take part in a medical research study. Before deciding whether you want to take part, you need to understand why the research is being done and what it will involve.**

**Please read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if you have any questions. Take time to decide whether you wish to take part.**

**If you need more information, please ask any of the doctors looking after you.**

**Thank you for reading this.**

# Some of Your Questions.

## Why Is The Study Being Done?

The research study is to improve our ability to assess rectal cancer and therefore to help clinical decisions. The study will compare scans taken prior to your operation with the results of the tissues removed. Comparing the two will enable us to see whether those pre-operative scans can predict the outcome of treatment.

## Why Have I Been Chosen?

In your hospital, Magnetic Resonance Imaging (MRI, or body-scanning) is always used to assess rectal cancer prior to treatment. All patients with rectal cancer in your hospital are therefore being asked to take part in the study.

## Will I Be Treated Differently?

You will not be receiving any extra or different care from your fellow patients if you take part in the study. The only difference is that we would follow your care and use your scans and results to aid our research.

## Do I Have To Take Part?

You do not have to take part. If you decide not to take part, your treatment will continue exactly as it was planned. If you decide to take part and later decide you want to withdraw, you are free to withdraw at any time and for any reason.

## What Will Happen If I Take Part?

We will re-examine your scans to compare these to the pathological results that you are given. We will then follow you through your care using your consultant's medical notes. You will not be asked to have any extra tests or scans. However, we may ask you to fill in a questionnaire at some time in the future.

## What Do I Have To Do?

Your consultant may ask you a few extra questions but we will get all the information that we need from your medical notes and scans. There are no restrictions placed on diet, exercise, alcohol or anything else by taking part in the study.

## What Are The Side Effects?

There are no side effects, as you will not receive any new or different treatments.

## Risks To Women?

There are no different risks to women.

## What Are The Benefits To Me?

There are no new benefits to you. The results of this study will allow a better planning of future patients' treatments.

## What If New Information Becomes Available?

Sometimes during a study new information becomes available. You will be informed of any such new findings about MRI, the study or the treatment. You will be told of any changes in the way the study is being done and of any identified risks to which you may be exposed.

## Will My Details Be Kept Confidential?

The information we obtain from your taking part in this study will not be given to anyone or used for any purposes without your consent, unless the law requires us to do so.

## What happens if I Agree To Take Part?

Should you agree to take part in this study, you will be given a study number and that will be used, together with your initials, to identify you for the study. During the study researchers and representatives of the regulatory authorities will look at the study records including your medical notes. This is to ensure that the study is being conducted to the highest possible standard. However, only your study number and initials will identify you on the records and in any publications. In this way confidentiality is maintained.

## Who Has Checked The Study?

The National Health Service Research Regulatory Body (COREC) has reviewed this study and allowed it to go ahead. The Local Ethics Committee in your hospital has also checked the study and given its ethical approval.

## Will My Tissue Be Retained?

As part of this study we will be keeping a small piece of the cancer to study further. This will be saved for future research into cancer growth and spread.

## Where Is The Study Being Done?

This study is done at 10 Hospital in the United Kingdom and European. These particular hospitals are the leading research hospital in this field. About 460 patients will be asked to participate.

## How Long Will My Role In This Study Last?

The study will take place whilst you are in hospital. It will not affect the length of your stay. We hope to have studied enough patients by the end of 2002.

## What Will Happen To The Results Of The Trial?

The results of the research will be published in a report and in a medical journal. You will not be identified in these publications.

## Who Is Organising And Funding The Trial?

The study is being run and funded by a registered charity, The Pelican Cancer Foundation.

## Where Can I Get My Questions Answered?

If you have any questions during the course of this research, or if you think you have an injury due to this study, please call Mr Ian Daniels (01256 314746). He is the Research Fellow and will be able to deal with any queries.

# The M.E.R.C.U.R.Y Project – Consent Form.

## Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study.

Patient Hospital Number: ……

Patient Initials: ……

Patient Identification Number: ……

**The patient should complete the whole of this sheet himself/herself.**

| | | | |
|---|---|---|---|
| Have you read the patient information sheet? | YES | | NO |
| (Please circle the answers) | | | |
| Have you had the opportunity to ask questions and discuss this study? | YES | | NO |
| | | | |
| Have you received satisfactory answers to all of your questions? | YES | | NO |
| | | | |
| Have you received enough information about the study? | YES | | NO |
| | | | |
| Do you understand that you are free to withdraw from the study: | | | |
| • At any time? | | | |
| • Without having to give reason for withdrawing? | | | |
| • And without affecting your future medical care? | YES | | NO |
| | | | |
| Do you agree to take part in this study? | YES | | NO |
| | | | |
| Do you allow a piece of your removed tissue to be used for further studies | YES | | NO |
| | | | |
| Do you allow us to record your progress after the surgery for five years | YES | | NO |
| | | | |

Name of Patient (block letters) Date Signature

Name of Surgeon Date Signature

## Appendix 2: Members of the Steering Group

| | | |
|---|---|---|
| Chairman | Dr John Fowler | (Medical Director – Pelican) |
| Study Coordinator | Mr Ian Daniels | (Research Fellow – Pelican) |
| Research Supervisor | Dr Gina Brown | (Radiologist – Royal Marsden Hospital) |
| Surgeon | Professor Bill Heald | (Surgical Director – Pelican) |
| Surgeon | Mr Brendan Moran | (Surgeon – Basingstoke) |
| Radiologist | Dr Delia Peppercorn | (Radiologist – Basingstoke) |
| Oncologist | Dr David Sebag-Montefiore | (Oncologist – Leeds) |
| Pathologist | Dr Phil Quirke | (Pathologist – Leeds) |
| Statistician | Dr Andy Norman | (Statistician – Royal Marsden Hospital) |
| Secretary | Ms Dianne Hayter | (Director – Pelican Centre) |

**Appendix 3a: MRI**

# MRI Reporting Proforma

Code No:
Eg BAS 1, ASP 1, EPS 1 etc

| | | |
|---|---|---|
| **Patient Name** | | |
| **Centre** | **MR Exam Number** | |
| | | |
| Exam technically satisfactory (3mm) | Yes | No |
| Has the patient received Radiotherapy | Yes | No |
| Has the patient had a previous rectal MRI | Yes | No |
| If Yes, date of previous examination | ……/……/…… | |

**Gross morphology and Infiltrating margin of extramural spread**

| | |
|---|---|
| Polypoidal | |
| Annular ulcerating | |
| Annular non-ulcerating | |
| Eroding | |
| Pushing | |
| Infiltrating | |

**Metastatic spread**

| | |
|---|---|
| Nodes demonstrated not suspicious | |
| Nodes demonstrated <3 suspicious | |
| *Nodes demonstrated ≥4 suspicious* | |
| *Extramural venous invasion* | |
| *Tumour deposits/satellites present* | |

**Local invasion**

| | | |
|---|---|---|
| Submucosa | T1 | |
| Muscularis | T2 | |
| Beyond Muscularis <1mm | T3a | |
| *Beyond Muscularis 1-5mm* | *T3b* | |
| *Beyond Muscularis 5-15mm* | *T3c* | |
| *Beyond Muscularis >15mm* | *T3d* | |
| *Into adjacent organs* | *T4a* | |
| *Perforation of visceral peritoneum* | *T4b* | |

**Margins**

| | |
|---|---|
| *Distance to mesorectal fascia <1mm* | *Me1* |
| Distance to mesorectal fascia >1mm | Me0 |
| *Low rectal tumour (below levator) >T2* | *MeSph* |

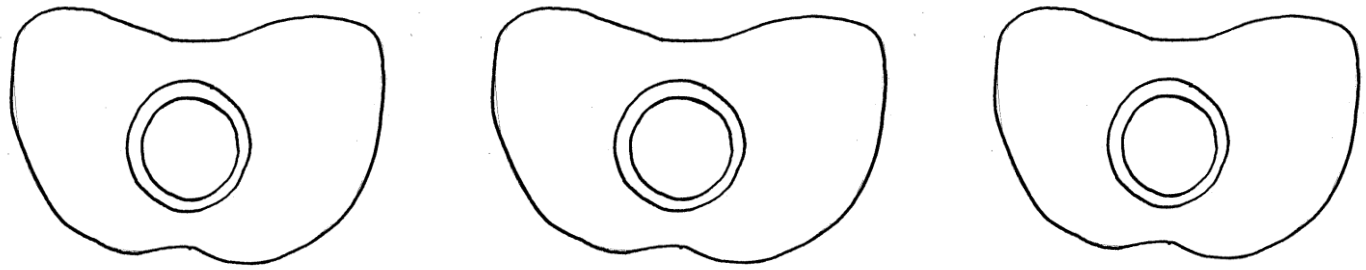
**Measurements**

| | |
|---|---|
| Maximum extramural spread | |
| Minimum distance to mesorectal fascia/potential CRM from outer edge of tumour | |
| Please state distance to CRM for: | |
| a. main tumour | mm |
| b. Suspicious lymph node | mm |
| c. Extramural veonus invasion | mm |
| d. Tumour satellite/deposit | mm |
| | |
| Distance to the sphincter (Low tumours only) | mm |
| | |

## Appendix 3b: MRI Proforma – Pathologist Targeting Form

### 1. Below the Tumour

**Right** **Left**



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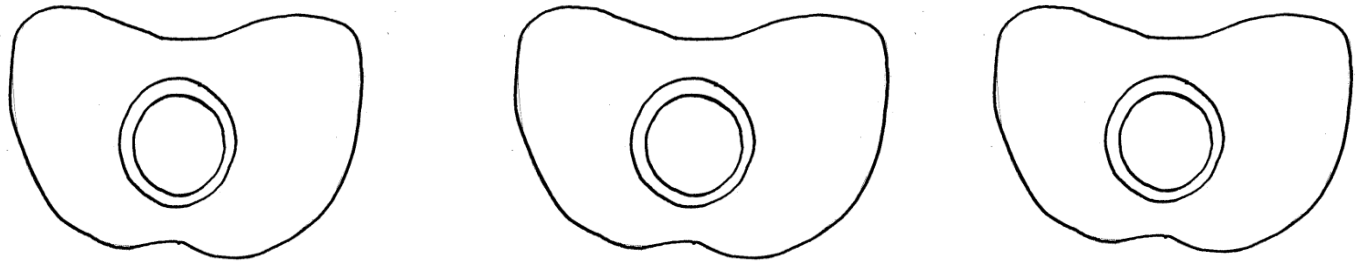
### 2. At the level of the Tumour

**Right** **Left**



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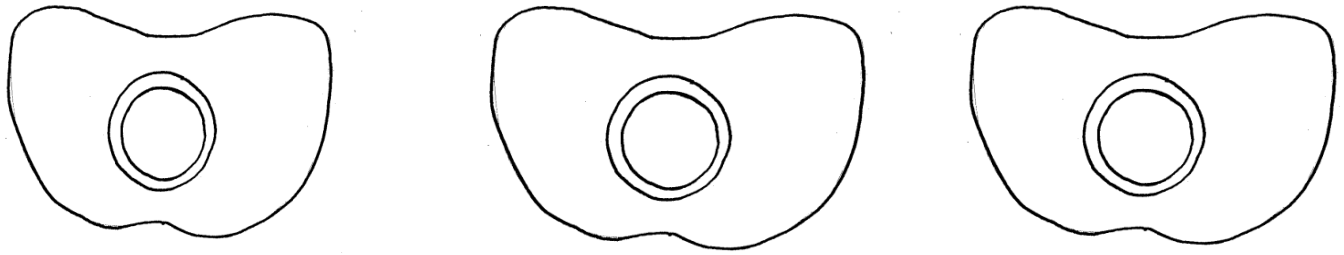
### 3. Above the Tumour

**Right** **Left**



---

**INCRESING HEIGHT FROM THE DISTAL RESECTION MARGIN**

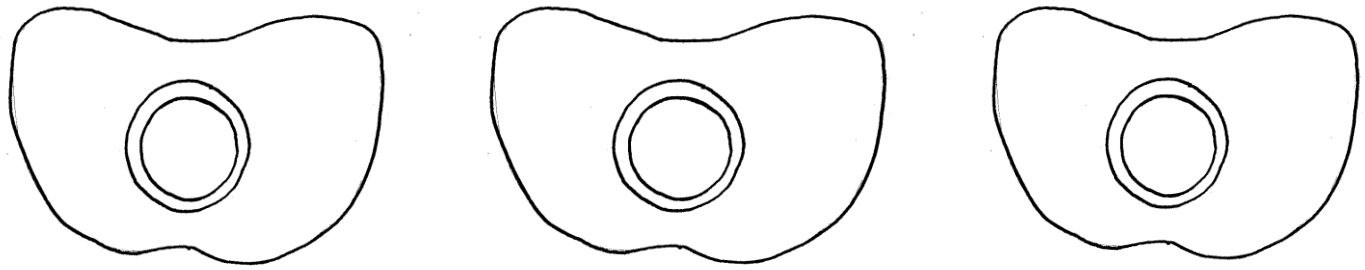
(Images taken looking from the patient's feet)

## Appendix 3b: MRI Proforma – Pathologist Targeting Form

**(Copy to remain with Form 1)**

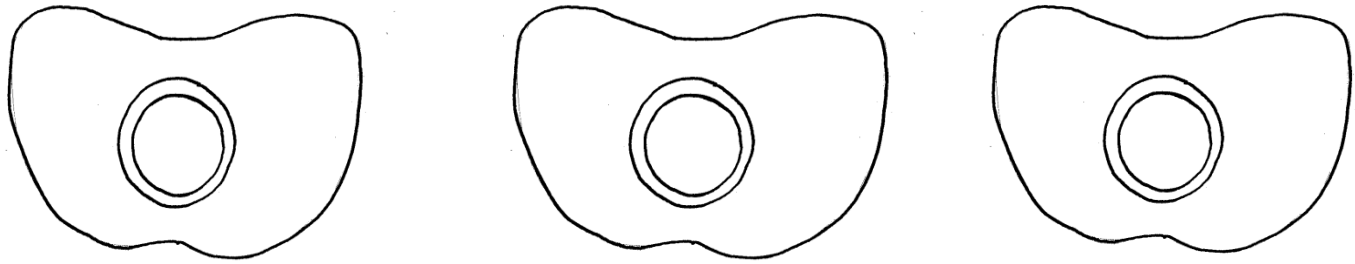
**1. Below the Tumour**

**Right** **Left**



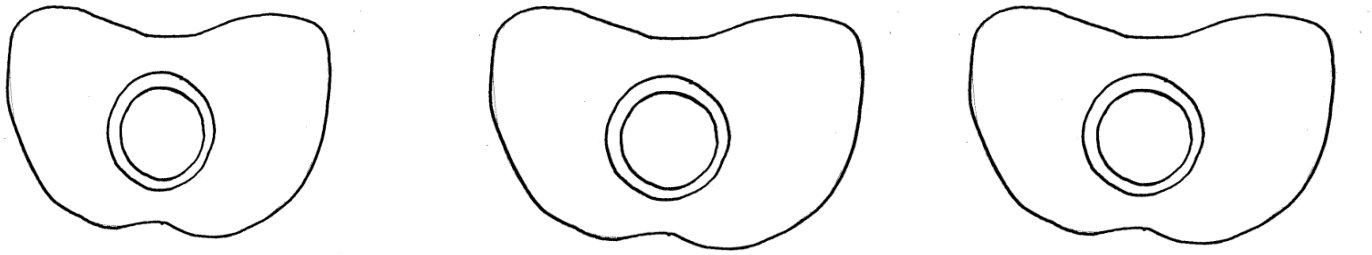
**2. At the level of the Tumour**

**Right** **Left**



**4. Above the Tumour**

**Right** **Left**



**INCRESING HEIGHT FROM THE DISTAL RESECTION MARGIN**

(Images taken looking from the patient's feet)

## Appendix 3c: MRI Proforma – Pathologist Targeting Form

**Please mark on the following diagrams** **(Tick if present)**

1. Tumour position…… ☐
2. Site of extramural spread if seen…… ☐
3. Sites of nodal deposits…… ☐
4. Sites of extramural vascular invasion…… ☐
5. Sites of extra-nodal tumour deposits…….. ☐
6. Sites of peritoneal perforation…… ☐
7. Sites of local invasion into adjacent organs…….. ☐
8. The site of closest tumour CRM…….. ☐
9. The site of closest CRM (Nodal etc)…….. ☐
10. Sites of extramural venous invasion (vessel >3mm dia)…..... ☐

## Appendix 3c: MRI Proforma – Pathologist Targeting Form

**(Copy to remain with Form 1)**

**Please mark on the following diagrams** **(Tick if present)**

1. Tumour position…… ☐
2. Site of extramural spread if seen…… ☐
3. Sites of nodal deposits…… ☐
4. Sites of extramural vascular invasion…… ☐
5. Sites of extra-nodal tumour deposits…… ☐
6. Sites of peritoneal perforation…… ☐
7. Sites of local invasion into adjacent organs…… ☐
8. The site of closest tumour CRM…… ☐
9. The site of closest CRM (Nodal etc)…… ☐
10. Sites of extramural venous invasion (vessel >3mm dia)…... ☐

# Appendix 4: Current Local Practice within the MDT

Hospital Surgical ……
Oncological ……

Members of the MDT Surgeons ……
……
……
Radiologists ……
……
Pathologists ……
……
Oncologist ……

## Current Protocols – Regarding Neo-adjuvant Therapy:

Do you use MRI to refine your decisions regarding pre-operative therapy for patients with rectal cancer?

Always Sometimes Never

Do you use Short-Course Radiotherapy (SCR) in patients with rectal cancer?

Always Sometimes Never

Do you use Long-Course Radiotherapy (LCR) in patients with rectal cancer?

Always Sometimes Never

Do you use Combined Chemo-Radiotherapy (CCR) in patients with rectal cancer?

Always Sometimes Never

If you use SCR please fill in Section 1.

If you use LCR please fill in Section 2.

If you use CCR please fill in Section 3.

## 1. Regarding Short-Course Radiotherapy (SCR).

| | | |
|---|---|---|
| Do you use this in all patients? | Yes | No |
| Do you use this in upper rectal cancers? | Yes | No |
| Do you use this in low rectal cancer? | Yes | No |
| Do you use this in patients who will undergo APE? | Yes | No |
| Do you use this in elderly patients only? | Yes | No |
| Do you use this in younger patients only? | Yes | No |
| Do you use this in cases where the CRM is threatened? | Yes | No |
| Do you have reservations about SCR? | Yes | No |

Please outline your current SCR Protocol on the Page provided

Short-Course Radiotherapy Protocol - ……..Hospital

## 2. Regarding Long-Course Radiotherapy (LCR)

| | | |
|---|---|---|
| Do you use this in all patients? | Yes | No |
| Do you use this in upper rectal cancers? | Yes | No |
| Do you use this in low rectal cancer? | Yes | No |
| Do you use this in patients who will undergo APE? | Yes | No |
| Do you use this in elderly patients only? | Yes | No |
| Do you use this in younger patients only? | Yes | No |
| Do you use this only in advanced T4 lesions | Yes | No |
| Do you use this in cases where the CRM is threatened? | Yes | No |
| Do you have reservations about LCR? | Yes | No |

Please outline your current LCR Protocol on the Page provided

Long-Course Radiotherapy Protocol - ……..Hospital

## 3. Regarding Combined Chemo-Radiotherapy

| | | |
|---|---|---|
| Do you use this in all patients? | Yes | No |
| Do you use this in upper rectal cancers? | Yes | No |
| Do you use this in low rectal cancer? | Yes | No |
| Do you use this in patients who will undergo APE? | Yes | No |
| Do you use this in elderly patients only? | Yes | No |
| Do you use this in younger patients only? | Yes | No |
| Do you use this only in advanced T4 lesions | Yes | No |
| Do you use this in cases where the CRM is threatened? | Yes | No |
| Do you have reservations about CCR? | Yes | No |

Please outline your current LCR Protocol on the Page provided

Combined Chemo-Radiotherapy Protocol - ……..Hospital

| Code No:<br>Eg BAS 1, ASP 1,<br>EPS 1 etc | Patient Registration Form | Patient<br>Addressograph |
|---|---|---|

## Appendix 5: Pre-MRI Form.

**Date of completion** ……/……/200…

**Family History of CRC** Yes [ ] No [ ]

**Consultant Surgeon** ……

**Sex** Male [ ] Female [ ] **Age** ……years

**Is this patient suitable for MRI assessment?** Yes [ ] No [ ]

**Pre-operative height above the anal verge on digital assessment** ..……cms

**Pre-operative height above the anal verge on sigmoidoscopic assessment** ..……cms

**Is the tumour?** Fixed [ ] Tethered [ ] Mobile [ ]

**Is the tumour?** Anterior quadrant [ ] Posterior quadrant [ ]

Left lateral quadrant [ ] Right lateral quadrant [ ]

**Is this patient fit for an operation to remove this tumour?** Yes [ ] No [ ]

Likely operation; Local Excision [ ] Anterior Resection [ ]

TME performed [ ] TME not performed [ ]

AP Excision [ ] Defunc$^{n}$. Colostomy [ ]

None of the above [ ] Other …….

**Wish of these adjuvant modalities would you prescribe based on this initial assessment?**

Short-course RT [ ] Long course RT [ ]

Chemo-RT [ ] None of the above [ ]

**Predicted operative difficulty relating to patient build and tumour position**

Straight forward [ ]

Moderately difficult [ ]

Difficult [ ]

**Has this patient signed a consent form?**

Code No:
Eg BAS 1, ASP 1,
EPS 1 etc

Multidisciplinary Team Decision Form

Addressograph

## Appendix 6: Post-MRI Form.

**Date of completion** ……/……/200… **Consultant Surgeon** ……

| | | | | |
|---|---|---|---|---|
| **Meeting Attendees** | Surgeon | [ ] | Radiologist | [ ] |
| | Oncologist | [ ] | Pathologist | [ ] |
| **Histology Report** | Adenocarcinoma | [ ] | Poor diff$^{n}$. | [ ] |
| | Other …… | | | |
| **Evidence of metastases** | Yes | [ ] | Liver | [ ] |
| | | | Lung | [ ] |
| | | | Peritoneal | [ ] |
| | | | Other …… | |
| | No | [ ] | | |

**Plan for pre-operative management**

| | | | | |
|---|---|---|---|---|
| | Short course RT | [ ] | Long course RT | [ ] |
| | Chemo-RT | [ ] | None | [ ] |
| **Operation Plan** | Local Excision | [ ] | Anterior Resection | [ ] |
| | TME performed | [ ] | TME not performed | [ ] |
| | AP Excision | [ ] | Defunc$^{n}$. Colostomy | [ ] |
| | None of the above | [ ] | Other ……. | |
| **Synchronous Disease** | Yes | [ ] | No | [ ] |

**Special Warnings from MRI for surgeons**

……..…
……..……
……

Code No:
Eg BAS 1, ASP 1,
EPS 1 etc

# Operation Details

Patient Addressograph

## Appendix7: Operation Details.

**Date of completion** ……/……/200…

**Consultant Surgeon** ……

**Operating Surgeon** Consultant [ ] Registrar [ ]

**Examination under anasthetic**: Height above anal verge ……cm

**Tumour position** Anterior quadrant [ ] Left lateral quadrant [ ]

Posterior quadrant [ ] Right lateral quadrant [ ]

**Metastatic disease at laparotomy** Yes [ ] No [ ]

**If yes, where?** Local [ ] Distant [ ]

**Operation performed** Local Excision [ ] Anterior Resection [ ]

TME performed [ ] TME not performed [ ]

AP Excision [ ] Defunc$^{n}$. Colostomy [ ]

None of the above [ ] Other …….

**Was this operation** Curative [ ] Palliative [ ]

**Surgeons assessment of specimen**

TME performed, mesorectal fascia intact [ ]

TME performed, mesorectal fascia breached [ ]

Surgically obvious margin involvement [ ]

**Has the patient been defunctioned?** Yes [ ] No [ ]

**Did the MRI influence whether the sphincters were preserved?**

Yes [ ] No [ ]

# Appendix 8: MRI Technique Criteria

## A8.1 Optimisation of MR technique used for patient imaging

The features that define image quality are the signal to noise ratio, speed of acquisition of images and resolution. Improvements in image quality have been achieved through technological developments. Such as stronger gradients and thus greater signal from the area to be scanned. In particular, coil design has advanced from using the body coil, within the magnetic gantry at a distance from the area being examined (with a relatively poor signal to noise ratio) to dedicated coils designed to maximise signal detected. An early advance in coil design was the endo-rectal coil that received signal at a point of direct contact with the bowel wall. Unfortunately, the role of endo-rectal imaging in the routine staging of rectal cancer is limited. As with any endo-luminal technique stenosis and structuring, pain, and discomfort, bowel wall motion, lesions in the upper rectum and coil migration hamper image acquisition. Recently, sophisticated multiple element surface coil arrays have been developed, designed to maximise signal to noise ratios over the region examined.

### A8.2 Patient Preparation

No bowel preparation, air insufflation or intravenous anti-spasmodic agents are used. Air insufflation and rectal contrast results in unacceptable image degradation due to deflation of distended bowel. Small bowel peristalsis does not produce image degradation, as small bowel is not within the field of view. Abdominal wall movement is a potential cause of motion artefact and image degradation but this may be eliminated by ensuring firm compression of the lower abdomen with the use of support pads as necessary beneath the pelvic wrap-around coil. This results in ‘splinting’ of lower abdominal wall excursion.

### A8.3 Image Sequence

#### A8.3.1 For a 1.5T MRI Scanner and pelvic phased array coil (Torso-type Coil)

Sequence1: After a coronal localiser, sagittal scans are required from inner pelvic sidewall to sidewall using a 24cm field of view, 5mm contiguous/interleaved slices (no gap), TR>2500 and <5000, TR=85. This acquisition will be used to plan high-resolution oblique axial images (Sequence 3).

Sequence 2: Axial T2-weighted fast spin-echo acquisitions of the anatomic pelvis by using a 24cm field of view, a 5mm contiguous section thickness, 4000/85, 512 x 256 matrix, an echo train length of eight, no fat saturation, a 32kHz bandwidth, and two signals acquisitions (2NEX).

Sequence 3: These are planned whilst sequence 2 is running. The sagittal T2 weighted images obtained are then used to planT2-weighted thin-section axial images through the rectal cancer and adjacent peri-rectal tissues. It is critical that these images are performed perpendicular to the long-axis of the rectum (See figure below). The images are obtained by using a 16cm field of view, a 3mm section thickness, no intersection gap, 4000/85, a 256 x 256 matrix, an echo train length of eight, no fat saturation, a 32kHz bandwidth and four acquisitions (4 NEX).

### A8.3.2 For a 1.0T MRI Scanner

Sequence 1: As above

Sequence 2: As above

Sequence 3: This is performed as above with a modification of the imaging parameters to obtain adequate SNR.

The high resolution images are obtained with 20cm field of view, 3mm section thickness, no intersection gap, a 256 x 256 matrix, a TR >2500 (ideally 5000), and a TE > 80 (ideally 136). A typical acquisition will take 12 minutes.

## A8.4 Low Rectal Tumours

Coronal imaging for low tumours

## A8.5 Image Collection

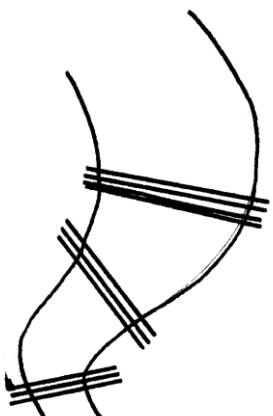
Once the MRI has been performed and reported the following sequences need to be reprinted for the study.

We need the high-resolution axial images of the tumour showing the section with the maximum extra-mural depth of invasion and the closest CRM on a 4-slice/page format to be submitted (1 sheet should suffice). It is critical for the success of the study that these images are axial to the rectum as they form the basis of the comparison to the pathological specimens (See Figure 1 below).

We need 1 mid-sagittal image for orientation with guidelines and one without guidelines for pelvimetry.

The remaining images needed (High Resolution Axials) could be submitted on a 16-20-images/sheet format.

Figure 1.Impression of the Orientation of MRI ‘Cuts’



Code No:
Eg BAS 1, ASP 1,
EPS 1 etc

# Appendix 9: Pathology Reporting Form

Initials …… Date of Birth …/…./..… Sex M F

Pathologist…… Surgeon…… Date……

## Macroscopic Assessment

Specimen Grade 1 2 3 **N**

Photographs Anterior ☐ Posterior ☐

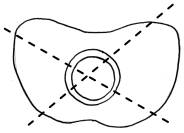
Tumour is ☐ above ☐ at ☐ below

the peritoneal reflection

Maximum tumour diameter …..cms Minimu

Presence of tumour perforation (pT4) Yes ☐ No ☐ Is the resection complete? Yes ☐ No ☐

Position of tumour



Distance to distal resection margin …..cms

Distance from the dentate line …..cms

Photograph of Sequential Slices Yes ☐ No ☐

Tumour involvement of proximal/distal margin Yes ☐ No ☐

## Histology

**Type:** Adenocarcinoma Yes ☐ No ☐

**Differentiation**: Poor ☐ Well/Mod ☐
(By predominate type)

**Local Invasion:**

Submucosa (pT1) ☐
Muscularis propria (pT2) ☐
Beyond Muscularis propria (pT3) ☐
Local invasion/peritoneal breach (pT4) ☐
Tumour perforation ☐

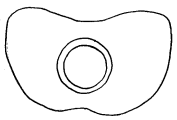
Maximum extramural spread of tumour or node …..mm

## Metastatic Spread

No of Nodes examined ….

No. of positive nodes ….

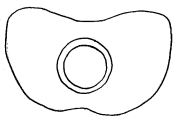
Apical Node positive Yes No



Involved node close to CRM Yes No

**Extramural Vascular invasion** Yes No

Invasion in vessel >3mm dia. Yes No



Extra-nodal deposits seen

Yes No

**Mark sites on diagrams**

Whole mount section
Closest CRM for tumour or node ☐

Whole mount section
Depth of invasion ☐

## Tumour Extent (Mucinous tumours)

Maximum extent of tumour ….mm

Maximum extent of tumour and mucinous componant …..mm

## Pathological Staging

**TNM** T ☐ N ☐ M ☐

**Dukes' Stage**

A ☐ B ☐ C1 ☐ C2 ☐

# Appendix 10 TNM Staging

## T Primary Tumour

Tx Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in-situ: intraepithelial or invasion of the lamina propria

T1 Tumour invades submucosa
T2 Tumour invades muscularis propria
T3 Tumour invades through muscularis propria into sub-serosa or into non-peritonealised or peri-rectal tissues
T4 Tumour directly invades other organs or structures and/or perforates visceral peritoneum.

## N Regional Lymph Nodes

Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in 1-3 peri-rectal lymph nodes
N2 Metastases in 4+ peri-rectal lymph nodes

## M Distant Metastases

Mx Presence of distant metastases cannot be assessed
M1 No distant metastases
M2 Distant metastases

| Stage | Stage Grouping | | | Dukes' Stage |
|---|---|---|---|---|
| Stage 0 | Tis | N0 | M0 | |
| Stage I | T1-2 | N0 | M0 | A |
| Stage II | T3-4 | N0 | M0 | B |
| Stage III | Any T | N1-2 | M0 | C |
| Stage IV | Any T | Any N | M1 | |

# Appendix 11: Independent Data Monitoring Committee

## Members

| | | |
|---|---|---|
| Mr W. H Allum | Consultant Surgeon | Epsom General Hospital, Epsom, Surrey<br>Royal Marsden Hospital, Sutton, Surrey |
| Mr R Ahearn | Medical Statistician | Royal Marsden Hospital, Sutton, Surrey |
| Dr R Huddart | Clinical Oncologist | Royal Marsden Hospital, Sutton, Surrey |

It is envisaged that this group would meet three twice during the period of the study.

Initially after 100 patients have been accrued so as to ensure that the aims of the study are being met and that the quality of the data is high.

Secondly at the end of the study, again to assess the quality of the data and to confirm that all objectives have been met and that the trial has been completed.

All members of this committee will have a copy of the protocol prior to commencement of the study.

## Appendix 12: Colorectal Nurse Checklist of Events

| | | Checklist | | | |
|---|---|---|---|---|---|
| **Step 1** | Newly diagnosed patient approached | | | | |
| **Step 2** | Patient consented | Yes | ☐ | No | ☐ |
| **Step 3** | Patient registered | Yes | ☐ | | |
| **Step 4** | Registration form completed by surgeon | Yes | ☐ | | |
| **Step 5:** | Phone date of MRI to centre | Yes | ☐ | | |
| **Step 5:** | MRI performed | | | | |
| **Step 6:** | MRI Proforma to Pathologist/Centre | | | | |
| **Step 7:** | MDM meeting - Proforma completed | Yes | ☐ | | |
| **Step 8:** | Phone date of surgery to centre | Yes | ☐ | | |
| **Step 9:** | Operation – Proforma completed | | | | |
| **Step 10:** | Pathology Proforma completed | | | | |
| **Step 11:** | Confirm patient discharge | Yes | ☐ | | |
| **Step 12:** | Is the patient registered for follow-up? | Yes | ☐ | No | ☐ |

**(If Yes, confirm with Pelican Centre and Follow-up Booklet will be issued)**