



Surgical Timing After Radiotherapy
for Rectal Cancer: Analysis of
Technique (STARRCAT)

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Chief Investigator - Mr N K Francis

CONTACT DETAILS

Chief Investigator Mr Nader Francis
Consultant Surgeon
Yeovil District Hospital NHS Foundation Trust
Yeovil
Somerset
BA21 4AT

Telephone: 01935 384244
Email: nader.francis@ydh.nhs.uk

Co-Investigators: Mr Reuben West
Consultant Surgeon
Weston General Hospital
Grange Road
Weston-super-Mare
BS23 4TQ

Telephone: 01934 881046
Email: reubenwest@nhs.net

Mr Ponnandai Arumugam
Consultant Surgeon
Royal Cornwall Hospital
Truro
Cornwall
TR1 3LJ

Telephone: 01872 255021
Email: ponnandai.arumugam@rcht.cornwall.nhs.uk

Mr Anthony Dixon
Consultant Surgeon
North Bristol NHS Trust
TrustHeadquarters
BeckspoolRoad
Frenchay
Bristol
BS16 1JE

Telephone: 0117 3406503
Email: anthony.dixon@nbt.nhs.uk

Mr Tom Edwards
Consultant Surgeon
Musgrove Park Hospital
Taunton
Somerset
TA1 5DA

Telephone: 01823 333444
Email: tom.edwards@tst.nhs.uk

Mr Rob Longman
Consultant Surgeon
UH Bristol Trust
Bristol Royal Infirmary
Upper Maudlin Street
Bristol
BS2 8HW

Telephone: 0117 3423066
Email: robert.longman@uhbristol.nhs.uk

Co-Investigator: Prof George Hanna
Imperial College
St Mary's Hospital
Praed Street
London
W2 1NY

Telephone: 020 7886 2125
Email: g.hanna@imperial.ac.uk

Statistics: Dr Paul Ewings
Research Design Service,
Taunton and Somerset Hospital
Taunton
Somerset
TA1 5DA

Telephone: 01823 342799
Email: paul.ewings@tst.nhs.uk

Pathology Dr Edwin Cooper
Consultant Histopathologist
Yeovil District Hospital NHS Foundation Trust
Yeovil
Somerset BA21 4AT

Telephone: 01935 384393
Email: edwin.cooper@ydh.nhs.uk

Radiology Dr Huw Roach
Consultant Radiologist
University Hospitals Bristol NHS Foundation Trust
Bristol Royal Infirmary
Marlborough Street
Bristol
BS2 8HW

Telephone: 0117 342 2728
Email: huw.roach@UHBristol.nhs.uk

Oncology Dr Stephen Falk
Consultant Clinical Oncologist
Bristol Haematology and Oncology Centre
Horfield Road
Bristol
BS2 8ED

Telephone: 0117 342 2461
Email: stephen.falk@uhbristol.nhs.uk

Research Fellow: Mr Jake Foster
Department of Research and Development
Yeovil District Hospital
Yeovil,
Somerset
BA21 4AT

Telephone: 01935 384559
Email: jake.foster@ydh.nhs.uk

Research Nurses: Mrs Jo Allison
Department of Research & Development
Yeovil District Hospital
Yeovil,
Somerset
BA21 4AT

Telephone: 01935 384297
Email: joanna.allison@ydh.nhs.uk

Mrs Adel Grey
Clinical Trials Nurse
MacMillan Unit (level 3)
Yeovil District Hospital
Yeovil,
Somerset
BA21 4AT

Telephone 01935 384934
Email: Adel.grey@ydh.nhs.uk

Trial Management: Mrs Barbara Williams-Yesson,
R&D & Clinical Trial Manager
Yeovil District Hospital
Yeovil
Somerset
BA21 4AT

Telephone: 01935 384559

Fax: 01935 384653

Email: barbara.williams-yesson@ydh.nhs.uk

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OVERVIEW

Surgery is the mainstay of treatment for rectal cancer, but the addition of neo-adjuvant chemo-radiotherapy (CRT) results in down-staging, decreased local recurrence and improved survival. However, radiotherapy also causes inflammation that makes surgery particularly challenging, which can have a detrimental effect on clinical outcomes. The ideal time interval between CRT and surgery has never been evaluated by robust evidence. Current practice for timing of surgery after CRT varies between 4 to 12 weeks after CRT, with little supporting evidence. However, the optimum timing should allow adequate time for resolution of the inflammatory changes and optimise tumour response. Thus enabling surgery to be less challenging and without compromising the oncological benefits of CRT.

The aim of this pilot study is to inform the planning of an RCT investigating the impact of timing after long course chemoradiotherapy (CRT) on surgical performance for patients with advanced rectal cancer. It is anticipated that up to 50 patients undergoing CRT will be recruited from 6 centres across the South/ South West of England to receive their surgery at either 6 weeks or 12 weeks after completion of CRT.

The main outcome measures of this pilot study are objective evaluation of operative technical difficulty, R0 resectability and down staging of disease.

BACKGROUND

Rectal cancer is the fifth most common cancer in men and the tenth most common in women in the United Kingdom. Approximately eight and a half thousand new cases were diagnosed in the UK in 2007 of which 61% were in men. In 2009, rectal cancers were responsible for 3531 deaths with a rate of 6.4 deaths/100,000 population in England and Wales. An additional 1404 deaths resulted from recto-sigmoid disease.(1)

Rectal cancer is potentially curable if diagnosed and treated at an early stage and surgery remains the mainstay of treatment, but it can be technically challenging. For cancers advanced at diagnosis, neo-adjuvant chemo-radiotherapy (CRT) results in down-staging of disease, decreased local recurrence and improved survival (2-6); however, inflammation and oedema following radiotherapy can make the surgery even more technically demanding. Outcomes in colorectal surgery in general are highly surgeon dependent, and increasing the technical difficulty of surgery has a detrimental effect on these outcomes (7-10). The complication rate (including anastomotic leak, pelvic sepsis, wound infection and post-operative death) is reported to be as high as 30% (11-13). These complications in turn prolong hospital stay and decrease quality of life for patients. An intervention capable of decreasing the surgical complexity of these cases has the potential to improve outcomes and reduce costs throughout the patient pathway.

The ideal time interval between CRT and surgery should allow time for resolution of the inflammatory changes caused by radiotherapy while optimising tumour response. This may result in improved rates of sphincter-preserving surgery, better nerve preservation and fewer intra- and post-operative complications. The need for a stoma is an important factor for patients and increased rates of sphincter preservation would improve patient quality of life and reduce length of stay because of the reduced need for stoma care education. NHS costs could be decreased as a result of reduced need for ongoing stoma care supplies. Nerve preservation is important in post operative

sexual function, especially in men, and these important nerves often pass through the inflamed tissues surrounding the rectum. Resolution of the inflammatory changes may make identification and preservation of these nerves easier, resulting in lower rates of sexual dysfunction.

Although some studies have shown beneficial effects from increasing the time between CRT and surgery, others have failed to show this. Evidence from large randomised trials is lacking in this area and the optimal time interval between CRT and surgery is still a contentious issue.(7-10;14-17) Surgery has traditionally been offered between 4 and 12 weeks after long course CRT but the choice is supported by scant clinical evidence.

Although the focus of this study is on evaluating the impact of delaying surgery on surgical complexity, it is important that a delay in surgery has no negative impact on oncological outcome and this will be an important outcome in the large trial. To investigate the potential impact of a delay in surgery on tumour response, an audit of cases of rectal resections meeting the eligibility criteria for the proposed trial was performed in Yeovil. It is limited by its small numbers and the fact that it is not randomised. However, it suggested that tumour response may be positively impacted by delaying surgery. A total of 24 cases were included, all of which had a diagnosis of adenocarcinoma. Ten resections were performed between 6 and 12 weeks after CRT (group A) and 14 at 12 weeks or more (group B). In group A, 5 specimens showed no marked regression and 5 showed minimal residual tumour. No cases had complete response (no residual tumour). In group B, 3 had a complete response, 8 had minimal residual tumour and 3 cases showed no marked regression (unpublished data from Yeovil).

STUDY AIM

The overall aim of the study is to test the feasibility of a definitive large randomised controlled trial by confirming its rationale and piloting all necessary components of that trial. The twin objectives are:

- (1) To assess the efficacy of an interval of 12 (rather than 6) weeks between CRT and surgery for the reduction of surgical technical complexity, and therefore surgical errors without any oncological compromise on the MRI.
- (2) To test processes and gather information for the planning of a large RCT investigating the impact of the timing of surgery (6 vs 12 weeks) on clinical outcomes following neo-adjuvant chemo-radiotherapy for locally advanced rectal cancer.

The aim of the future large RCT will be to assess the clinical and cost-effectiveness of delaying surgery following neo-adjuvant chemo-radiotherapy for patients with locally advanced rectal cancer. It will include a number of important clinical and quality of life outcomes, which are included here so that the pilot mirrors as closely as possible the intended future larger trial.

METHODS

Study Design

This is a pilot randomised controlled trial involving 5 centres across the Avon, Somerset and Wiltshire Cancer Services Network (ASWCS) and a further centre

from a neighbouring network. The network performs 300 rectal resections each year, of which approximately 30% will be eligible for recruitment. Collaboration between the centres already takes place with regional multi-disciplinary teams and co-operation between surgeons in the network.

Patients will be approached during their initial oncology appointment prior to receiving neo-adjuvant chemo-radiotherapy (CRT) and subsequent surgery for rectal cancer. They will be consented prior to commencing CRT, and will be randomised to receive surgery at either 6 or 12 weeks after completion of CRT. Short term outcomes will be captured during the hospital stay, and at 30 days. Patients' experiences will be captured through in-depth interviews. The patient pathway is summarised in the flow chart in annex 4.1.

It is anticipated that 50 patients from 6 centres undergoing elective rectal surgery (either anterior resection with Total Mesorectal Excision (TME) or abdomino-perineal excision (APE) for locally advanced rectal cancer will be randomised to receive surgery either:

Arm A n = 25 patients

6 weeks delay post standard neo-adjuvant CRT before surgery

Arm B n = 25 patients

12 weeks delay post neo-adjuvant CRT before surgery

Mode of surgery (open or laparoscopic) will be left to discretion of the surgeon. All patients will be cared for post-operatively within an enhanced recovery programme.

Short term outcomes will be captured during hospital stay and at 4 weeks follow up. Long term outcomes will not be captured during this feasibility trial.

Endpoints

Primary End Points

Joint primary outcomes are proposed:

- Surgical:
 - Complexity measurement by analysis of video recorded operations using structured check-list (annex 4.2)
- Oncological:
 - R0 resectability and quality of pathological specimen (including margins and perforations)

Secondary End Points

- Down staging of disease as assessed on magnetic resonance imaging (MRI) at 6 and/ or 12 weeks
- In-hospital surgical complications as defined by Dindo et al (see table 1)
- Sphincter preservation
- Quality of life measure using C-30, CR-29 and EQ-5D questionnaires
- Length of hospital stay
- 30-day re-admission and mortality

- Psychological impact on patients because of the length of surgical delay
- **Quantitative assessment of tumor cell density**

Inclusion Criteria

- Age 18 years or over
- Completing neo-adjuvant long-course CRT for rectal cancer
- Fit for surgical resection by open or laparoscopic anterior resection or abdomino-perineal resection (APR)
- American Society of Anaesthesiology (ASA) grades I, II and III
- Able and willing to provide written consent

Exclusion Criteria

- Emergency admission or bowel obstruction/perforation
- Short course radiotherapy
- Anal cancer
- Metastatic disease
- Previous palliative pelvic radiotherapy
- Rectal cancer on top of inflammatory bowel disease
- Contra-indication to MRI
- Poor cognitive ability and/or unable to provide consent
- Pregnancy

Recruitment

Patients will be identified at Colorectal Multi-Disciplinary Team meetings and outpatient clinics. Potentially eligible patients will be identified at the MDT by the surgeons/ oncologists and will be informed of the trial prior to CRT by a research nurse at the surgery or oncology clinic, who will discuss the study with the patient and answer any questions. Patients will be given a written Participant Information Sheet (Appendix 1) to take away. If willing and eligibility is confirmed, written consent will be obtained (Appendix 2) by the principal investigator (PI) of each site or appropriately delegated research staff member and the patient randomised. Patients are to be consented and randomised prior to commencing CRT. This allows them and their families to have a clear picture of their treatment pathway at the outset, and allows participating sites the optimal length of time for scheduling of operations and scans. Rates of patients not completing CRT as prescribed are very low (<5%) and so drop-out rates are not thought to be high during CRT. Following completion of CRT, some patients will feel physically and emotionally drained, and so consent at that time would be more burdensome for patients.

If, at any time, a patient wishes to withdraw their consent surgery will take place at the earliest opportunity.

Randomisation

The randomisation schedules will be prepared by the trial statistician. A computerised random number generator will create permuted blocks of variable size, with randomisation stratified by site and type of surgery TME or APE and open vs laparoscopic.

Allocation to trial arm will be determined by central telephone randomisation, ensuring maintenance of allocation concealment. A unique trial number will be allocated and group allocation will be confirmed via email to the surgeon, research nurse and the oncologist. Patients will be informed of the randomisation result by letter and telephone by the Research nurse of the unit, which will also contain the standard operation date and details of admission per local policy.

Neoadjuvant Therapy

All patients will receive an MRI of the pelvis prior to commencing neo-adjuvant CRT: standard care for rectal cancer patients.

Neo-adjuvant long course chemo-radiotherapy should proceed as follows:

Radiotherapy – 45 GY in 25 fractions over 5 weeks with Capecitabine according to ASWCS protocol

Planning and treatment should be as for the ARISTOTLE trial and concurrent participation in the ARISTOTLE trial is permissible. The protocol for the ARISTOTLE study involves randomising patients to receiving either the above regime or receiving irinotecan 60 mg/m² intravenously (IV) once weekly, for weeks 1 - 4 and capecitabine 650 mg/m² orally twice daily Monday to Friday for five weeks with radiotherapy 45 Gy in 25 fractions.

Awaiting Surgery and Downstaging MRI

Surgery will take place after the allotted time. Complications of neoadjuvant therapy such as bowel obstruction, will result in expedited review by the surgical or medical teams, as appropriate. If patients require surgery for diversion or resection to relieve their obstruction prior to their allocated timing, patients are allowed to remain in the trial but analysed separately.

Post neo-adjuvant treatment MRI will be required in this study at 6 weeks for all patients and at 12 weeks for the 12 weeks treatment arm. This may be an additional investigation to routine practice in some centres. The repeat MRI will be analysed by the nominated radiologist of the study (HR) by comparison with the pre-CRT MRI and reporting tumour size and down staging. Timing of this second MRI scan close to the date of surgery will allow data collected during this study to be correlated with tumour response found during histological examination, and used to develop a three-point scale (i) progression, no response, (ii) partial, fibrosis/ reduction in size and (iii) complete response/ fibrosis. This three-point scale is similar to that used to assess pathological tumour response for the assessment of tumour down-staging on MRI.

Surgery

This study involves surgery for low rectal cancer including Total Mesorectal Excision (TME) or Abdomino-Perineal Excision (APE). Mode of surgery (open or laparoscopic) will be left to the discretion of the surgeon. All perioperative care will proceed as per local practice. Laparoscopic TME and the abdominal part of APE will be video recorded using standard digital capture equipment. Open operations will be digital video recorded using a sterile laparoscope held by the research fellow who will “scrub-in” and wear sterile gloves and gown. The perineal part of APE will be digitally video recorded using head-mounted cameras or a sterile laparoscope held

by the research fellow. The perineal part of APE will be reconstructed according to each unit's policy. Postoperative recovery will be carried out as per local unit practice, although key elements of enhanced recovery will be encouraged in this study.

Patients will be discharged once standard discharge criteria are met:

- Tolerating normal oral diet
- Mobilising independently
- Comfortable on oral analgesics
- Confident and independent with their stoma care, with help as appropriate

Patients will be reviewed at 4 weeks postoperatively at either inpatient or outpatient appointments to capture postoperative morbidity.

Blinding

Blinding of the patient, surgeon, oncologist and research nurse is not feasible in this study. However, those responsible for the main outcome assessments will remain blinded. Although it is very difficult to blind the research fellow to the randomisation arms of the study, the analysis of the videos for intra-operative complexity remains anonymous. Each recorded DVD will be allocated a unique trial number for the analysis. The same number will be allocated to the pathology and MRI results for each patient in order to maintain the blinding for the radiology and pathology assessment of outcomes.

OUTCOME MEASURES

Outcome measures will be recorded during the inpatient stay and at two week follow up. Complications (during the initial hospital stay or during the re-admission), re-admissions and deaths will be captured up to 30 days. The outcomes are as follows:

1. Operative technical difficulty

Surgical technical difficulty will be assessed by objective blinded assessment of intra-operative complexity using the digital recordings of all operative procedures. Mesorectal dissection will be recorded for both anterior resection and APE using the standard laparoscopic recording equipment available at participating centres. For open procedures, and perineal dissections of APE, recording of operative performance will be carried out using a sterile laparoscope held by the research fellow. The use of the frequency of items of operative complexity within the operation as a proxy measure allows assessment of the potential of delayed surgery to improve patient outcomes. To assess the impact of the timing of surgery on surgical complexities/near-miss rate, a standardised measure will be used. We have developed a structured check-list (Appendix 8) by adapting a tool developed to assess surgical performance in the national training programme for laparoscopic colorectal surgery (18).

A task analysis will be carried out involving dividing the operation into steps and sub-steps. The check-list will be used to identify encountered items of technical complexity during each step in the procedure. The tasks of TME and the abdominal part of APE are dissection of the vascular pedicle and dissection along the TME planes anteriorly, posteriorly and laterally. For the perineal part of the APE, two

additional tasks will be included in the analysis (perineal dissection and perineal closure).

Additionally, for each task mandatory steps have been identified. Deviation from these mandatory steps or any inappropriate interaction with the tissues will constitute an item of complexity. The items of operative complexity will be categorised based on Human Reliability Assessment techniques (18).

2. R0 resection status

Recorded by both the surgeon at the time of operation, and the pathologist following histological examination for microscopic tumour remnants at the resection margins.

3. Down staging of disease on MRI

Assessed radiologically by comparison of pre-CRT and pre-operative MRI. The pre-operative MRI will provide information regarding tumour size and threatened margins that may affect surgical approach. Post treatment MRI will be carried out at 6 weeks for all patients in order to ensure that delaying surgery would not compromise the oncological outcomes in the 12 weeks arm. The latter group will have another MRI scan close to the date of surgery to allow data to be correlated with tumour response found during histological examination. This will help to define the best timing of MRI after CRT. A three-point scale (similar to that used to assess pathological tumour response) will be used for the assessment of tumour down-staging on MRI.

4. Tumour response to chemo-radiotherapy

Assessed using standard histopathological techniques and categorised on a three-point scale as follows:

- a) No residual tumour cells and/or mucus lakes only
- b) Minimal residual tumour i.e. only occasional microscopic tumour foci identified with difficulty
- c) No marked regression.

5. Quality of resection specimen

Standardised high definition photography of the specimens from several, defined angles (see below) and histopathological cross-sections at a number of levels will be performed. The completeness of resection is defined by the integrity of the mesorectal fascia.

In addition, still photographs of the pelvis will be taken after removal of the specimen. The specimen photographs and digital image of the pelvis after resections will be sent to Yeovil to be assessed by the research fellow and the pathologist (EC) on a Likert-type scale to evaluate radicality of resection. They will also be used by the pathologist to identify key landmarks in the dissection field and aid interpretation of the specimen (19, 20).

The photographic "angles" of the resected specimens are:

- 1) anterior surface of specimen

- 2) posterior surface of specimen
- 3) close up of mesorectal surface to highlight any defects that would affect the scoring of the mesorectal assessment
- 4) after cutting 3mm slices through the tumour these are laid out and photographed
- 5) If applicable, a close up photograph is taken of a transverse section of tumour showing the surrounding mesorectal tissue (again to highlight any defects that would affect the scoring of the mesorectal assessment)

6. Sphincter preservation

Sphincter preserving surgery will be defined as cases in which there is sufficient rectal stump for colorectal anastomosis.

7. Operative complexity questionnaire

At the end of each procedure, the operating surgeon will complete a surgery complexity form to assess the perceived complexity and technical difficulty of the procedure. The questionnaire is based on the task analysis steps used for the operative video analysis and uses visual analogue scoring (Appendix 9).

8. Complications

All complications occurring in hospital (index stay or re-admission) will be recorded up to 30 days, based on Dindo classifications of complications:

Table 1; Classification of Surgical Complications (21)

Grade	Definition
Grade I	Any deviation from normal post operative course without the need of pharmacological or surgical intervention
Grade II	Require pharmacological treatment
Grade III	Require surgical, endoscopic or radiological intervention
Grade IV	Life threatening complication/ requiring ICU management
Grade V	Death of a patient

Specific reporting on the following complications within 30 days:

- Conversion to open operation
- Intra-operative haemorrhage
- Anastomotic leak
- Perineal wound dehiscence
- Perineal wound sinus/fistula
- Perineal wound infection
- Pelvic abscess

9. Length of hospital stay after surgery (counting day of surgery as day 0)

10. Re-admission within 30 days of surgery

11. Quantitative assessment of Tumor Cell Density (TCD)

The rectal cancer specimens will be prepared and reported by the histopathology department at the hospital providing the patient's care. Glass slides will be prepared as is standard for the analysis of pathology specimens. Once this reporting is complete, we will arrange for the transfer of the glass slides to St James Hospital, Leeds for analysis of tumour cell density (22). The slides will be digitally scanned at 400x magnification onto a computer. Using a digital slide viewer, a 9 mm² area will be selected in the region of greatest TCD and a systematic random sample of 300 points superimposed using virtual graticule software. TCD will be expressed as the percentage of points falling on tumour cells out of all the informative points. Following this scanning, the slides will be returned to the NHS hospital providing the patients' care for storage as they would for slides from all other patients.

12. Quality of life

Using EQ-5D-5L (Appendix 5) and EORTC QLQ-C30 & CR29 (Appendix 6) questionnaires. These will be completed:

- pre-operatively (at outpatient clinic when the patient has consented for the trial)
- postoperatively prior to discharge from hospital.
- postoperatively at 2 week follow-up outpatient clinic appointment.

DATA COLLECTION

Standardised Case Report Forms (CRFs) have been developed for the purpose of data capture. Separate forms for collection of pre-operative demographic data, pathological data and radiological assessment data will be used to record outcomes. They will be completed by the research nurse or appropriate consultant. Quality of life measures will be completed by the patient with the help of a research nurse as necessary at three time points, to allow assessment of the impact of the timing of surgery on recovery of pre-operative quality of life. A surgery complexity form will be completed by the surgeon at the end of the operation. This will include data about resection, sphincter preservation and operative complexity. Surgical complications, length of stay and re-admissions will be captured retrospectively from patient notes by the research nurse.

In order to record operations at each participating site, the research fellow will require a letter of access to be arranged at each site. A research passport will be organised by the sponsor. The research fellow will only record operations at these sites for the purposes of this research, and will have no role in the delivery of any form of clinical care at these institutions. The research fellow holds a substantive contract with the sponsor for the duration of the research trial.

SAMPLE SIZE

The sample size is guided by the twin aims of the proposal: to provide sufficient power to detect whether the delay in surgery achieves its short-term goal of reducing the complexity of the surgery; and to provide sufficient information to aid the planning of the future trial. A previous study assessing surgeons performing 61 rectal resections (23) found an average of 99 complexity items or near misses per operation, with a SD of 30. We believe the delayed surgery will reduce this number dramatically, perhaps by half. Conservatively, a reduction of 30 would require 22 patients per group to give 90% power using a 5% t-test. Allowing for post-randomisation exclusions, we aim to recruit 25 patients into each arm of the study giving a sample size of 50 patients.

DATA ANALYSIS

A CONSORT flow chart will be used to summarise trial participation, with reasons for ineligibility, refusal, drop-out and loss to follow-up recorded as far as possible. Descriptive measures on baseline data and outcomes will be presented, for example means, standard deviations, proportions etc., with confidence intervals. Formal comparative analysis between groups will be restricted to the number of operative errors, with planning for the full trial contingent on finding a significant difference. This will be based on the intention-to-treat principle. Inspection of the data mentioned above suggests a t-test may be suitable, or ANCOVA controlling for stratification factors; if not then alternatives such as Poisson regression will be considered.

PATIENT EXPERIENCE

In-depth semi-structured interviews will be conducted with a sample of approximately 20 patients, in their homes 4-8 weeks after discharge. They will be sampled purposively to include patients in both trial arms, from all sites, undergoing open and laparoscopic surgery and, where possible, patients refusing to participate in the trial but consenting to such an interview. A topic guide has been developed (Appendix 4) to explore aspects of the patients' experiences of participating in the trial (or not), to include in particular their feelings about being randomised and what aspects encouraged (or discouraged) them from participating. Interviews will be recorded and transcribed verbatim for analysis. Constant comparison techniques (24) will be employed to identify themes, with the aim of aiding the planning of successful recruitment and retention in the future larger trial. The research fellow will conduct this work under supervision by a qualitative researcher at Imperial College.

As recall of anxiety levels may be biased when assessed retrospectively, prospective collection of information regarding the level of anxiety caused by the intervention is desirable. Self-reported visual analogue scales are a quick, validated method of quantifying anxiety (25). We intend to ask those patients who are to be interviewed after their surgery to complete a visual analogue assessment scale at the time of their preadmission clinic appointment (approximately 2 weeks prior to surgery) to inform the degree of anxiety caused by having their surgery scheduled by the randomisation to the time that they are to have it. This additional task will help to provide quantitative data about the effect that the intervention of the trial has upon patient wellbeing, and supplement the information provided by the interviews.

ANALYSIS OF COSTS

Additional costs of this study will be covered by this research including any additional MRI scan. The future larger trial will include a full assessment of cost-effectiveness. There are not expected to be any differences in the two trial arms in terms of delivering the intervention, since it is simply about the timing of surgery. The drivers for marginal differences in costs are likely to arise in the differential complications arising from surgery. Data on these complications are captured in this pilot, and there are no other cost-related data requiring consideration at this stage.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) will be reported to the chief investigator within 24 hours of a member of the research team becoming aware of the SAE using the standard SAE report form (Appendix 10). This will be faxed to a safe haven fax (01935 384653) in the research and development office at Yeovil District Hospital. The investigator will make an assessment of intensity, causality, expectedness and seriousness. At the conclusion to the trial, all adverse events will be subjected to statistical analysis, and the conclusions of this included in the study report.

In this study and adverse event would be considered serious if it: a) results in death; b) is life threatening' c) requires prolongation of existing hospitalisation (excluding prolongation of admission for social or administrative reasons); or d) results in persistent or significant disability or incapacity. The research team will only notify fatal an unexpected non-fatal SAEs to the sponsor. The following adverse events are considered "expected" for this trial:

- Anastamotic leakage (clinical or radiological)
- Atelectasis
- Peri-operative myocardial infarction or cardiac arrhythmias
- Deep vein thrombosis / Pulmonary embolism
- Intestinal obstruction
- Intra-abdominal abscess
- Intra-abdominal haemorrhage
- Iatrogenic injury of any intra-abdominal organ
- Post-operative haemorrhage
- Respiratory tract infection
- Sepsis
- Stoma related complications
- Stroke / Transient ischaemic attack
- Urinary tract infection
- Wound dehiscence
- Wound infection

The Chief Investigator will provide the main REC with copies of all SAE reports.

DISSEMINATION

The findings will be written up for publication in a peer reviewed journal and presented at relevant national conferences for both medical and nursing staff, in order to raise awareness for the larger trial. Finally, the outcome of this project would be described during educational events organised by the R&D Department

PATIENT AND PUBLIC INVOLVEMENT

This research project has been discussed with them and they are very supportive. The potential benefits to patients have been explained and the group will be represented in the project steering committee, which will consist of members of the research project and the wider ERP team.

Additionally, this application has been considered by the local Patient Public Involvement (PPI) Group prior to submission. Two members of this group have been invited to sit on the Study Steering Group and will be involved in overseeing the conduct of the study.

Both of these groups have been involved in the project from the design stage, and have been particularly active in the design of the patient information leaflet.

ETHICAL and REGULATORY STANDARDS

The trial will be coordinated by the STARRCAT Trial Office at Yeovil District Hospital NHS Foundation Trust. The trial committee will obtain NHS REC, NHS R&D and Site-specific ethical approval prior to commencing research activities.

SPONSORSHIP

Yeovil District Hospital NHS Foundation Trust will be the Sponsor for this study.

QUALITY ASSURANCE

All study sites taking part in the trial will be required to attend a start-up meeting, detailing all aspects of the trial to ensure consistency in methodology across participating sites. All surgeons who have been invited to participate in the trial are experienced colorectal surgeons who have been selected as they are highly skilled trainers with significant experience in performing the operations being analysed in this study.

All investigators who have contact with patients as part of this trial will have received training in good clinical practice.

PROJECT MANAGEMENT

The project will be co-ordinated by the Research Fellow supported by the Yeovil District Hospital NHS Foundation Trust R&D Manager. A STARRCAT Research Nurse has been appointed to manage the day to day aspects of patient care for the duration of the study.

The project will be overseen by the Trial Steering Committee (TSC) and the Trial Management Group (TMG). The committee will meet at each time point on the Gantt chart (Appendix 11). Minutes of meetings will be taken and will detail study progress

and timelines, staff appointments, recruitment targets and data quality and well as training and education.

Financial management is organised in collaboration with the Trust Finance Department and there is a designated Research Finance Assistant.

For this project, staff will be appointed, trained and line managed by the Trust R&D Manager who will also be responsible for setting and adhering to study timelines. Patient follow-up, data collection and database entry will be key responsibilities of the R&D Department in addition to monitoring and preparing data for analysis, report writing and subsequent publication.

APPENDICES

Appendix 1 – Patient Information Sheet

Appendix 2 – Consent Form

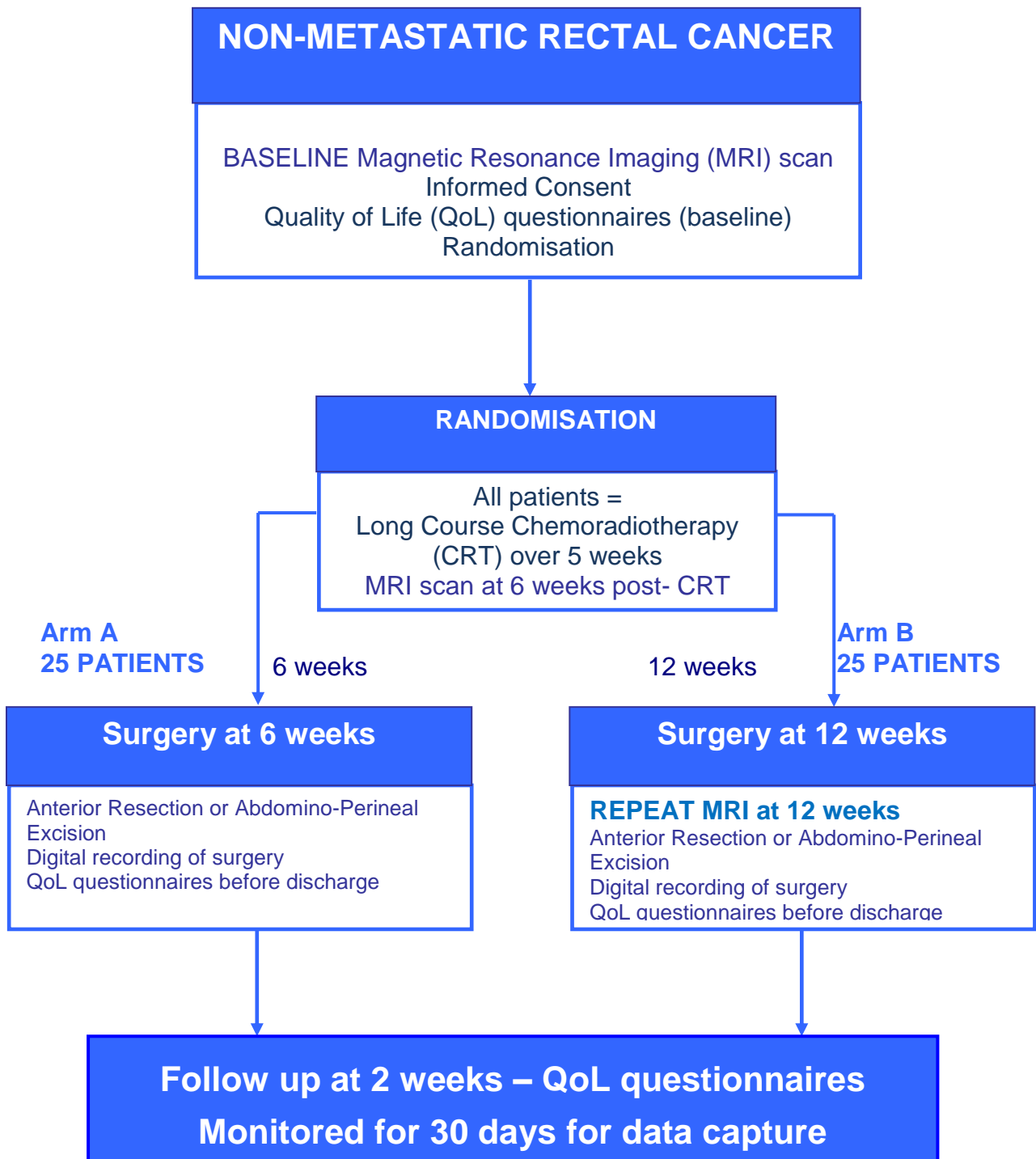
Appendix 3 – GP / Clinician information letter

Appendix 4 – Schedule for Interviews

Appendix 5 – QLQ-5D-5L Quality of Life Questionnaire

Appendix 6 – EORTC C30 and CR29 Quality of Life Questionnaires

STARRCAT FLOW CHART



Appendix 8 – Task analysis

APE task analysis

	Task area	Task	Start point	Aim
1	Dissection of vascular pedicle	Dissection around vascular pedicle	Incision of peritoneum and creation of window	Main vessel(s) sufficiently skeletonised at adequate level, landmarks (ureter, duodenum) defined
		Trans-section of vessel	Clip-applier, vascular stapler or tissue _mobilization dissection device appears on screen	Vessel(s) secured and transsected
2	TME	Posterior/lateral mobilization	Entry into posterior TME plane	Rectum released posteriorly and laterally. Nerves protected, TME plane respected
		Anterior mobilization	Incision of anterior peritoneal pouch	Rectum released anteriorly. Structures (vagina, seminal vesicles) protected, TME plane respected
3	Perineum	Patient Positioning	Prone jack knife	Safe position with good exposure
		Incision	Identification of landmarks	Skin incision with appropriate clearance
		Enter peritoneum posteriorly	Coccygeal resection	Adequate clearance and good exposure
		Lateral dissection	Extra-levator retraction and _mobilization of rectum	Identification and preservation of nerves
		Evacuation of specimen	Eversion of specimen leaving anterior attachment	Safe evacuation without rupture or avulsion
		Anterior dissection	Clearance from prostate/vagina	Adequate tumour clearance with no bowel perforation
4	Closure A: Mesh closure B: Flap Closure	Mesh repair of peritoneal defect	Placement of mesh	Secure mesh fixation to fascial tissue
		Flap dissection	Identification of pedicle	Safe _mobilisation with no vascular compromise
		Flap reconstruction	Flap rotation and repositioning	Closure of peritoneum with viable flap tissue

Anterior resection task analysis

	Task area	Task	Start point	Aim
1	Dissection of vascular pedicle	Dissection around vascular pedicle	Incision of peritoneum and creation of window	Main vessel(s) sufficiently skeletonised at adequate level, landmarks (ureter, duodenum) defined
		Trans-section of vessel	Clip-applier, vascular stapler or tissue energising dissection device appears on screen	Vessel(s) secured and transsected
2	TME	Posterior/lateral mobilization	Entry into posterior TME plane	Rectum released posteriorly and laterally. Nerves protected, TME plane respected
		Anterior mobilization	Incision of anterior peritoneal pouch	Rectum released anteriorly. Structures (vagina, seminal vesicles) protected, TME plane respected

Appendix 9 – Surgical complexity questionnaire

Surgical Complexity Survey Abdomino-perineal resection/ Anterior resectoin

1. How radical was the operation? Please circle the appropriate answer.

R0 R1 R2

2. Was sphincter sparing surgery performed?

Yes

No

3. a) Was a stoma formed?

Yes

No

b) What type of stoma?

4. Visualisation of the nerves

Could you visualise the autonomic nerves?

Yes

No

Please indicate the complexity of the individual steps on the scales below 0 = least complex and 100 = most complex

Dissection of the Vascular pedicle

a) Dissection around vascular pedicle

0 _____ 100

b) Trans-section of vessel

0 _____ 100

TME

a) Posterior/lateral mobilization

0 _____ 100

b) Anterior mobilization

0 _____ 100

Perineum (APR only)

a) Patient Positioning

0 _____ 100

b) Incision

0 _____ 100

c) Enter peritoneum posteriorly

0 _____ 100

d) Lateral dissection

0 _____ 100

e) Evacuation of specimen

0 _____ 100

f) Anterior dissection

0 _____ 100

Closure (APR only)

A: Mesh closure

Mesh repair of peritoneal defect

0 _____ 100

B: Flap closure

Flap dissection

0 _____ 100

Flap reconstruction

0 _____ 100

Adverse Events Reporting Form

Patient Identification

Patient Full Name: _____ STARRCAT Trial Number: _____
Date of Birth: dd/mm/yyyy Hospital Number: _____ NHS Number: _____
Responsible Surgeon: _____
Hospital: _____

SAE Description

Date of event: _____

Outcome: Recovered Continuing

Please provide further information if event continuing:

Was event fatal or life-threatening? Yes No Date of Death: dd/mm/yyyy

Details of adverse event: _____

Did the event require hospitalisation? Yes No Number of days: _____

Relation to treatment

Do you consider the SAE to be: Definitely related to treatment Probably related to treatment
Probably not related to treatment

Reasons: _____

Name of reporting person: _____ Position: _____

Telephone Number: _____ Date: dd/mm/yyyy

Signature: _____ Email: _____

Appendix 11 – Gantt Chart

Package 1 Preliminaries (months -3 to 3) Finalise study protocol, complete necessary forms to submit through IRAS to REC and Trust RM&G departments. Appoint research fellow and research nurses (in conjunction with ASWCS and Western CLRN)

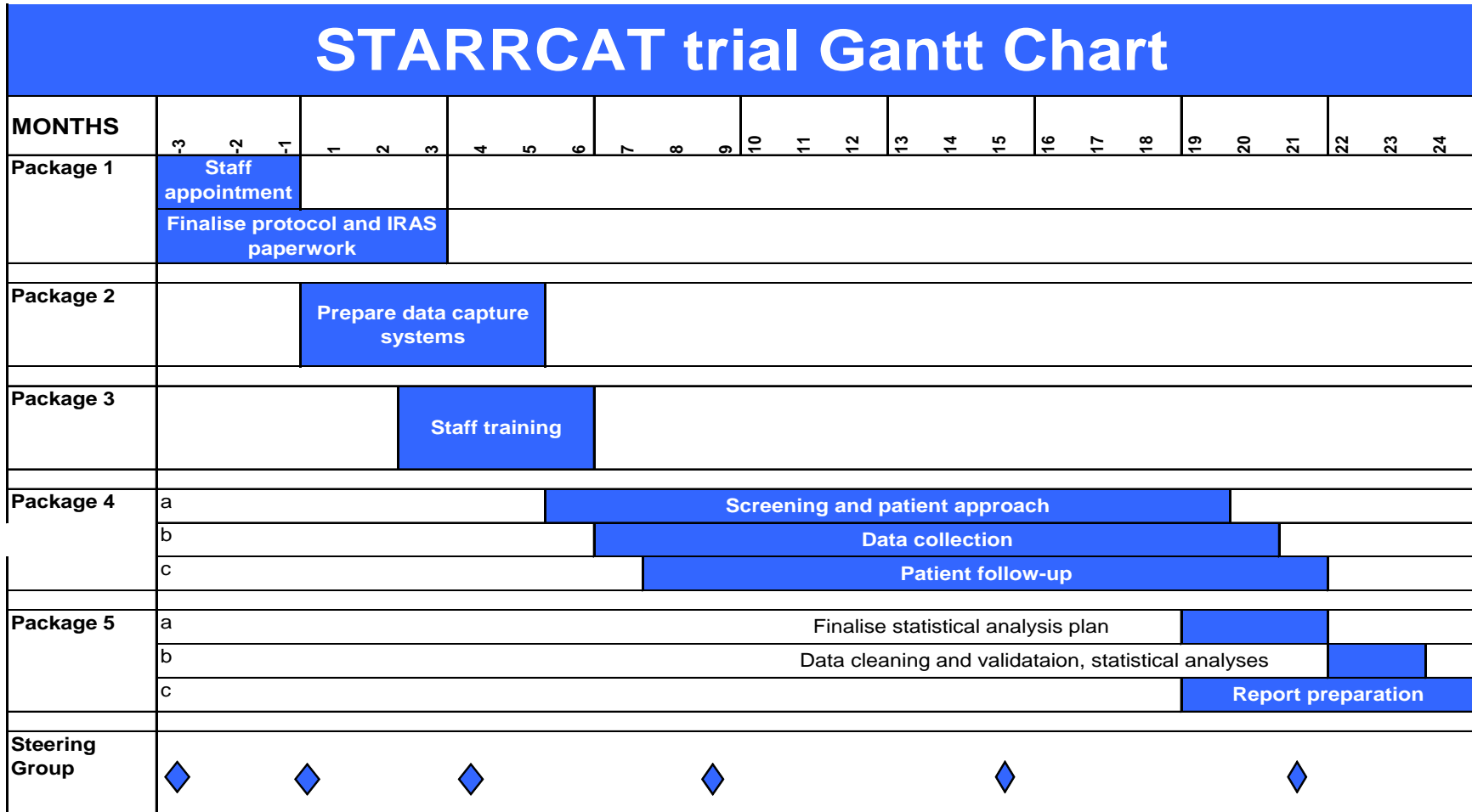
Package 2 Prepare data capture systems (months 1 to 5) Develop trial paperwork (CRFs etc), design database, set up trial master file and individual site files.

Package 3 Training (months 3 to 6) Train staff at participating sites

Package 4 Main fieldwork (months 7 to 21) Identify and approach potential participants, recruit and randomise eligible and willing patients, collect in-hospital data and follow up to 30 days. Code and enter data onto bespoke database.

Package 5 Analyses and reporting (months 19 to 24) Finalise statistical analysis plan, undertake data cleaning and validation, undertake statistical analyses, prepare report and publications.

Appendix 11 – Gantt Chart



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