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PROSPeCT

The PROSPeCT study: Improving the prediction of metastatic disease in primary colorectal cancer: Prospective multicentre evaluation of a prognostic model of conventional predictive variables and novel variables derived from perfusion computed tomography

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ISD Cancer Clinical Trials Team
Edinburgh

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Protocol authorised by:

Name:_____ Role in Trial: Chief Investigator

Signature:_____ Date:_____

KEY CONTACTS

Chief Investigator: Dr Vicky Goh
St Thomas' Hospital
Email:

Sponsor: King's College London
Funder: National Institute for Health Research Health Technology Assessment programme

Trial Coordinator: Michelle McDermaid

ISD Cancer Clinical Trials Team, (Partner in CaCTUS - Cancer Clinical Trials Unit Scotland),
Gyle Square,
1 South Gyle Crescent,
Edinburgh, EH12 9EB.
0131 275 6538

michelle.mcdermaid@nhs.net

Trial Statistician: Susan Mallett
CR-UK Centre for Statistics in Medicine, Oxford
Email: susan.mallet@csm.ox.ac.uk

Investigators:

Professor Steve Halligan

Professor Ken Miles

Dr Rob Glynne-Jones

Professor Doug Altman

Dr Susan Mallett

Dr Stuart Taylor

Dr Ashley Groves

Dr Manuel Rodriguez Justo

Independent trial steering committee:

Professor Andrea Rockall (Professor of Cancer Imaging, Barts and the Royal London Hospital)

Dr David Miles (Oncologist)

Sue Judge (Patient Representative)

Professor Clive Bartram (Radiologist)

Data Monitoring Committee:

Dr Allan Hackshaw (Chair)

Professor Peter Hoskin

Participating sites (listed alphabetically) and local PI contact details

Site	Cancer Network	Local PI	Contact details
Bradford Teaching Hospitals NHS Trust	Yorkshire	A Lowe	Andy.lowe@bradfordhospitals.nhs.uk
East and North Herts NHS Trust+	Mount Vernon	R Glynne-Jones	Rob.glynnejones@nhs.net
Guys and St Thomas's NHS Trust+	South East London	A Jones	Annette.f.jones@gstt.nhs.uk
Imperial College Healthcare NHS Trust+	West London	D Blunt	d.blunt@imperial.nhs.uk
Lothian University Hospitals NHS Trust	Scottish	J Brush	John.brush@luht.scot.nhs.uk
North Staffordshire University Hospital NHS Trust	Greater Midlands	I Britton	Ingrid.britton@uhns.nhs.uk
Nottingham University Hospitals NHS Trust+	Mid Trent	R Dhingsa	dhingsar@yahoo.com
Oxford Radcliffe Hospitals NHS Trust*	Thames Valley	A Slater	Andrew.slater@orh.nhs.uk
Portsmouth Hospitals NHS Trust*	Central South Coast	A Higginson	Antony.higginson@porthosp.nhs.uk
Royal Cornwall Hospitals NHS Trust, Truro	Peninsula	N Dodds	Nicholas.dodds@rcht.cornwall.nhs.uk
Sheffield Teaching Hospitals NHS Trust	North Trent	J Hampton	James.hampton@sth.nhs.uk
Southampton University Hospitals NHS Trust	Central South Coast	D Breen C Grierson	david.breen@suht.swest.nhs.uk Catherine.grierson@suht.swest.nhs.uk
Tayside Hospitals NHS Trust	Scottish	I Zealey	ian.zealley@nhs.net
University College Hospital NHS Foundation Trust+	North London	S Taylor	csytaylor@yahoo.com
York Hospitals NHS Foundation Trust	Yorkshire	R Mannion	Richard.mannion@york.nhs.uk
Leeds Teaching Hospitals NHS Trust	Yorkshire	D Tolan	djmtolan@doctors.org
*pilot sites +reserve sites			

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1. Research objectives

1.1 Primary objective

To improve the prediction of metastatic disease in patients with colorectal cancer by developing a prognostic model based on disease free survival, that is superior to current practice, via prospective evaluation of both conventional predictive variables and novel variables derived from Perfusion CT.

1.2 Secondary objectives

1. To improve the predictive value of variables that are currently used in standard practice (e.g. T and N stage) for metastatic disease via prospective development and evaluation of a predictive model constructed using leading-edge statistical modeling.
    - We will compare the prognostic model of standard predictive variables (i.e. without Perfusion CT parameters) with Stage grouping (High risk: ASC stage III), by change in proportion of patients who will be correctly predicted to develop metastasis

2. To assess the added value of using novel Perfusion CT parameters to predict metastasis by their addition to the prognostic model via comparison of best prognostic model with Perfusion CT parameters included, with the best prognostic model without Perfusion CT parameters. This will be performed for a) disease free survival and b) overall survival at 3 years

3. To compare prognostic models using a combined composite score of CT perfusion parameters with a simpler combination of CT perfusion parameters (e.g. single parameters or pair). The simplest model with sufficient precision will facilitate clinical applicability of a prognostic model.

4. To assess the added value of including pathology measures in the best prognostic model developed within this grant, to predict development of metastasis. Pathology measures will be included (a) as a combined composite score or (b) in simpler combinations such as in pairs.

We expect to assess the following: presence of macroscopic vascular invasion; involvement of the resection margin at surgery; regression score post chemoradiation; immunohistochemistry: CD105, VEGF, Glut-1, K-ras status, microsatellite instability

5. To determine the variability of CT Perfusion variables to estimate whether the limits of agreement are clinically acceptable at 1) local centres and 2) central review. Sources of variation related to both the observer (e.g. intra- and inter-observer variability) and the technical acquisition of CT data (e.g. scanner type, analysis software) will be examined.

6. To improve prediction of best prognostic model with CT parameters measurements from central review

   We expect a large improvement in prediction when central review Perfusion CT measurements are used, but this is not the primary outcome as this is further from clinical practice. However if this is of value and hospital centre based measurements are not, then the concept of using CT measurements is sound.

7. To examine the impact on the model operational cutpoint for risk, of different weightings of the clinical and patient assigned values for (a) correct prediction of an additional patient with metastasis and (b) one less patient given a false prediction of metastasis.
   We will use pure and mixed focus groups and a discrete choice experiment to explore the effects of hypothetical correct prediction of one additional patient with metastasis versus varying numbers of false-positive diagnoses in order to derive clinical and patient assigned weighting values.

8. To improve the prediction of metastatic disease in patients with colorectal cancer by the developing prognostic models using an extended 60 month follow up for overall survival (based on Office of National Statistics (ONS) data), as opposed to 36 month follow up for other models.

9. To explore the potential relationships between CT perfusion parameters and pathology characteristics in the tumours:

   These pathological characteristics will include tumor stage, macroscopic vascular invasion; regression score post chemoradiation; immunohistochemistry: CD105, VEGF, Glut-1, K-ras status, microsatellite instability

2 Background

2.1 Colorectal cancer

Colorectal cancer is one of the commonest causes of cancer death worldwide. In the UK there are approximately 37,500 new cases annually [1]. Up to 50% of patients still die from their disease ultimately. Surgery remains the mainstay of curative treatment, and refinement in surgical technique, e.g. total mesorectal excision (TME) for rectal cancer, has improved local recurrence rate [2]. However distant relapse rates have remained relatively stable despite 'potentially curative' surgery, with up to 50% developing metastases by 5 years [3]. Ultimate patient outcome is very poor once metastases are present with a 3% 5-yr survival. A better understanding of the biology of colorectal cancer has resulted in a shift in therapeutic focus. Firstly, novel chemotherapeutic agents have been developed e.g. anti-angiogenic drugs such as Bevacizumab, targeted at vascular endothelial growth factor (VEGF) and targeted agents such as Cetuximab, targeted at epidermal growth factor receptor (EGFR). Secondly, chemotherapy has shifted from the post-operative (adjuvant) to pre-operative (neoadjuvant) setting (under investigation in the FOxTROT trial). These advances have the potential to enhance patient survival, but have highlighted a need for better identification of high risk patients when initial staging is performed, especially the subgroup of Stage II/Dukes'B patients who would not usually be offered chemotherapy as standard care. Traditionally, adjuvant chemotherapy has been standard of care for patients with Stage III/Dukes' C disease [4,5]. There still is no consensus as to how patients with Stage II/Dukes' B disease should be treated [6,7] with a wide variation in local practice in the UK NHS.

2.2 Limitations of current staging

Accurate colorectal cancer staging is important as it estimates prognosis and determines the appropriate course of treatment. Currently, whole body computed tomography (CT) is the standard test for detecting metastases while MRI is performed additionally for regional staging of rectal cancer. Following imaging, 80% of patients have surgery intended to cure, but up to 50% relapse subsequently, peaking at 1.5 years [3]. The challenge for imaging is to better identify these 'high-risk' patients at their initial staging. The TNM-Stage grouping/Dukes' classification systems are widely used in clinical practice but have significant limitations. For example, Stage II/Dukes' B amalgamates cancers that have not spread significantly beyond bowel wall (T3) with very advanced tumours that invade adjacent organs (T4). As a result these patients have a widely differing final outcome despite being assigned the 'same' stage. The ability to detect patients at high risk of metastases at an earlier time point is important for earlier initiation of surgical/medical intervention, particularly with the paradigm shift from post-to pre-operative chemotherapy described above, and will inevitably impact on final outcome.

2.3 What constitutes a high risk patient?

Current prognostic markers are anatomically-based, the most widely applied being tumour extent, presence/absence of nodal disease, and presence/absence of distant metastases i.e. “stage” (TNM/Stage grouping or Dukes’ classification). A patient’s prognosis is poorer with higher T stage, presence of nodal disease and presence of metastatic disease. Other imaging and/or pathological features are also potential prognostic indicators, including tumour extension >5mm beyond the bowel wall, tumour distance from the potential surgical resection margin, presence of macroscopic vascular invasion, involvement of the resection margin at surgery and regression score post chemoradiation [8-10]. These have yet to be investigated systematically via prospective study of a prognostic model, one of the objectives of our study.

2.4 Perfusion CT may improve prediction of subsequent metastatic disease

The addition of Perfusion CT to standard preoperative staging may improve current identification of high risk patients. Perfusion CT is a short CT sequence (approximately 1 minute) which provides functional information regarding tumour perfusion and angiogenesis that is additional to the structural information provided by conventional CT [11-18]. Kinetic modeling, using software integrated into standard commercial reporting workstations that are in use in the NHS, is used to derive quantitative measures of tumour perfusion, blood volume and permeability surface area product (Figure 1).

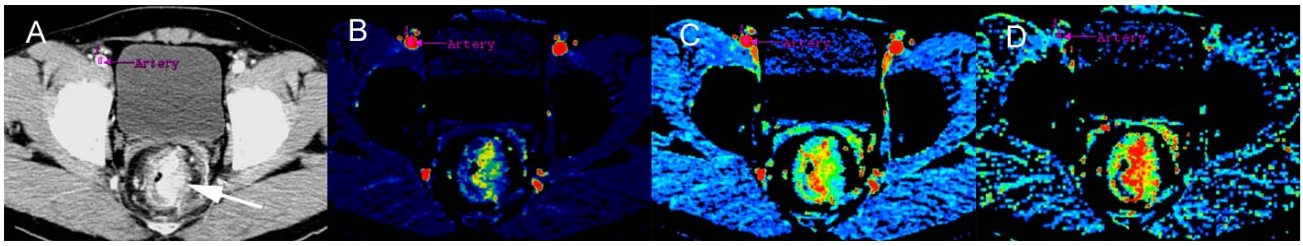


Figure 1. Rectal cancer (A, arrow) showing heterogeneous tumour perfusion (B), blood volume (C) & permeability(D) on the parametric maps derived from kinetic analysis of the Perfusion CT data

In the NHS, perfusion CT is used for guiding therapy following stroke. It has also been used by oncologists to evaluate novel anti-cancer drugs [19-23], including those directed at colorectal cancer [23]. Pilot data from our group has demonstrated that poorly perfused colorectal cancers are more likely to metastasize following surgery, irrespective of their initial stage [24], with a

difference in progression free survival. We hypothesize that this reflects relative tumour hypoxia, which is supported by evidence from other cancers [25,26].

Statistical analysis of our existing data, in preparation for this HTA submission, using a multivariate Cox model has indicated that Perfusion CT has potential to improve the identification of high risk patients at their initial staging. These findings require validation in a large number of patients across a number of NHS settings. Given the pressing clinical need to better identify these patients, we believe this hypothesis warrants further study in a multicentre setting in order to achieve significant power for a prognostic model including Perfusion CT parameters to be developed and evaluated. Importantly, Perfusion CT is a simple test that can be incorporated easily into standard staging CT but may have important health benefit and cost-saving implications to the NHS by better directing patient care.

2.5 Why is a prognostic model the most appropriate method in this setting?

Development of a prognostic model enables identification of the risk factors that are influential in predicting patient outcome and the use of these factors in a **systematic, reproducible** and **evidence based manner**. The goal of a prognostic model is to provide quantitative knowledge about the probability of outcomes in a defined patient population, for patients with different characteristics [27-29]. Models are ideally developed from a prospective patient study, using a combination of prior knowledge of the disease and judicious and informed use of statistical methods to diminish the likelihood of a flawed or biased models. Thus a prognostic model is the most appropriate means to answer the research question:

"Is the prediction of metastatic disease & survival obtained by Perfusion CT during primary colorectal cancer staging superior to standard imaging and pathological staging?"

2.6 Form of final rule

The prognostic model including Perfusion CT measurements will be used to develop a prognostic scoring rule. Our final rule will be transparent, evidence-based and simple. The final rule will be given in the form:

Prognostic score = a.Tstage + b.Nstage + c. Perfusion_ CT_measurements + d.other_variable,

where a, b, c and d are coefficients from the Cox model

This prognostic score will be used to predict patients at high risk, who are predicted to develop metastasis. The value of including Perfusion CT measurements in the prognostic score will be

assessed based on the change in patients with a correct and incorrect diagnosis compared to predictions made using current clinical practice rules to predict metastasis. The primary outcome will be expressed as two metrics, the change in sensitivity and the change in specificity both adjusted for prevalence of metastasis.

We will assess different relative weightings of sensitivity and specificity, based on the clinical importance of correctly predicting an additional patient with metastasis, compared to an additional patient without metastasis. Even excellent predictive models will generate false-positive and false-negative results, and the importance that patients and their doctors assign to these will vary, but is usually ignored. We therefore need to establish the range of weightings ascribed by both users and clinicians in order to determine the perceived value of the model in practice. We will obtain these estimates via pure and mixed focus groups of NHS users (patients, doctors, nurses, members of the general public) to explore attitudes towards the relative benefits of correct and incorrect prediction by the model of patients with metastasis. We will then use a discrete choice approach, again targeted at NHS users (patients, doctors, nurses, members of the general public), who will be asked to state their preferred scenarios from the range offered in order to establish utilities that turn on the potential range of true- and false-positive diagnoses offered by the model. Lastly, we will then examine the effect of these different weightings on the predictive value of the operational cutpoint for risk groupings in our model. This will be developed as part of another NIHR programme grant (RP-PG-0407-10338; PI Prof Steve Halligan).

3 Research design

Development and evaluation of a prognostic model via a prospective multicentre observational cohort study.
370 patients will be recruited over fifteen months from 10 - 20 UK sites. Participants will be followed-up for 36 months.

4 Centre selection

Each participating Centre (and local investigator) has been identified on the basis of:

- NHS setting (district general or teaching hospital) with large case load of colorectal cancer patients (>150 patients per year), reflecting a typical population and range of NHS practice
- Following an initial submission of interest via the British Society of Gastrointestinal and Abdominal Radiology (BSGAR) research network in January 2009, the principal investigator for each site (member of BSGAR, colorectal imaging lead) has indicated a

willingness to participate in the study, agreed to the study protocol, and to liase with other members of the patient management team.

- Successful scoping pilot in July 2009 for study design and planning: to identify referral patterns to CT, number of potentially eligible patients and ability to achieve study end-points at each site.
- Acknowledgement to conform to the administrative/ethical requirements and responsibilities of the study e.g. Good Clinical Practice
- BSGAR has an excellent previous track record for recruiting to studies of imaging interventions - HTA 02/02/01 randomised 5,548 patients - with close working relationships and practices.

Final inclusion of each participating centre will be confirmed once there is:

- Positive SSA by Local Research Ethics Committee (LREC)
- Local Research and Development (R&D) approval & signed Research Site Agreement

Site	Local PI	Cancer Network	No. of cases/yr	No. CT scanners	Manufacturer /Detector rows	CT capacity /day
Bradford Teaching Hospitals NHS Trust	A Lowe	Yorkshire	155	2	GE Healthcare 16-64	25/scanner
East and North Herts NHS Trust+	R Glynne-Jones	Mount Vernon	150	1	Siemens 64 Dual Source	28/scanner
Guys and St Thomas's NHS Trust+		South East London	200	3	Phillips 128	30/scanner
Imperial College Healthcare NHS Trust+	D Blunt	West London	250	>3	Siemens 128	40/scanner
Lothian University Hospitals NHS Trust	J Brush	Scottish	480	>3	Toshiba Siemens 16-320	30/scanner
North Staffordshire University Hospital NHS Trust	I Britton	Greater Midlands	284	3	Siemens 16	40/scanner
Nottingham University Hospitals+ NHS Trust+	R Dhingsa	Mid Trent	380	3	Phillips 16	20/scanner
Oxford Radcliffe Hospitals NHS Trust*	A Slater	Thames Valley	370	>3	GE Healthcare 16-64	20/scanner
Portsmouth Hospitals NHS Trust*	A Higginson	Central South Coast	314	3	Siemens 16-32	25/scanner
Royal Cornwall Hospitals NHS Trust, Truro	N Dodds	Peninsula	346	3	GE Healthcare 16-64	30/scanner
Sheffield Teaching Hospitals NHS Trust	J Hampton	North Trent	370	>3	GE Healthcare 32-64	30/scanner
Southampton University Hospitals NHS Trust	D Breen C Grierson	Central South Coast	300	2	Siemens 64	30/scanner
Tayside Hospitals NHS Trust	I Zealley	Scottish	340	3	GE Healthcare 64	25/scanner
University College Hospital NHS Foundation Trust	S Taylor	North London	250	3	Siemens 64	30/scanner
York Hospitals NHS Foundation Trust	R Mannion	Yorkshire	215	1	Siemens 16	25/scanner

*Pilot sites for the study at which trial materials, protocols and procedures will be piloted before roll out to remaining sites. +Initial reserve sites for the study which will be opened up if recruitment is poor.

Ten sites provide the optimal balance between a need to achieve adequate accrual and the marginal cost of each centre. We have identified a further 5 sites willing to participate if recruitment at any of the sites above is deemed inadequate/unacceptable by the data monitoring committee (DMC) once the trial begins.

5 Ethical issues

5.1 Ethical approval

Ethical approval from the National Research Ethics Service Committee will be applied for through the Integrated Research Application System (IRAS) and will be needed before the study can start.

The trial will be carried out according to guidelines of good clinical practice (GCP) as defined by paragraph 28 and Schedule 1 Part 2 of the Medicines for Human Use (Clinical Trials) Regulations, 2004, and the Clinical Trials Directive (2001/20/EC) elsewhere in the European Union and follow the principles of research governance.

The use and storage of human tissue will be carried out in accordance with The Human Tissue Act (2004) and The Human Tissue (Scotland) Act (2006). Human Tissues is defined as any material which has come from a human body, that consists of, or includes human cells and includes blood and other bodily fluids.

5.2 Risks & anticipated benefits for participants, including how benefits justify risks.

The risks associated with this study, additional to the standard risks of a contrast enhanced CT, which each participant undergoes as part of standard staging, are the additional radiation dose of the perfusion CT sequence itself, and administration of intravenous Buscopan, an antispasmodic used routinely in Radiology departments for luminal gastrointestinal studies. There is a risk of carcinogenesis associated with increased radiation exposure but this is highly dependent on dose and the age of the patient. The average annual natural background radiation dose in the UK is 2.2mSv. The dose constraint (limit) of 20mSv applied for the additional Perfusion CT acquisition is equivalent to 9.1 years of exposure to natural background radiation. This 20mSv dose is equivalent to one and a half whole body CTs, which patients will undergo as yearly surveillance following their surgery, and must be taken in the context of the carcinogenesis risk associated with anti-cancer medication and radiotherapy also. We believe the benefits of the additional

quantitative information (tumour perfusion and angiogenesis) that will be provided by Perfusion CT substantially outweighs any risks. Supporting this, we and other researchers have successfully applied for ethical permission for this procedure in the recent past.

6 Study population

6.1 Inclusion criteria

- Patients with suspected or proven (via optical colonoscopy and biopsy) colorectal cancer attending for pre-operative staging CT.
- Suspicion of colorectal cancer defined as:
    - Presence of a mass highly-suspicious for colorectal cancer on barium enema, CT colonography or other imaging
    - +/- large bowel obstruction
    - +/- elevated serum CEA
- Ability to provide informed written consent.
- Aged 18 years or over

6.2 Exclusion criteria

- Inability to provide informed written consent
- Pregnancy
- Renal impairment defined as serum creatinine >150mmol/L; previous iodinated contrast allergy
- Inability to cannulate
- Inability to lie flat
- Weight greater than 200 kg (maximum weight capacity of CT scanner is 200kg)

6.3 Subsequent participant withdrawal

In consenting to the trial, participants are consenting to the additional perfusion CT examination, perfusion CT data analysis, follow-up and data collection. If a patient withdraws subsequently, we will ask whether the trials unit may use information already collected or whether the patient explicitly also withdraws consent for this.

7 Enrolment

7.1 Identification of patients

Patients will be identified by the local principal investigator (and/or clinical team) via:

- Triage of CT request forms:

  - All CT requests require justification by an IRMER practitioner (Ionising Regulations [Medical Exposures] Regulation, amended 2006) and will be vetted by the radiologist at each site
- Colorectal multidisciplinary team (MDT) meeting
  - All colorectal cancer patients are discussed at the MDT at each of the sites identified.
- NCRN colorectal nurse practitioner

After identification potentially eligible participants will be invited to take part in the trial. The process of invitation will be via an invitation letter and Patient Information Sheet (PIS), which will be sent with the CT appointment letter. Patients will usually have at least 24 hours to consider participating in the trial.

7.2 Informed consent process

7.2.1 For planned CT examinations

Informed consent will be obtained from all participating patients, and will be undertaken by the principal investigator (or delegate: radiologist, radiographer or member of the clinical team trained and competent in obtaining consent) at each centre when the patient attends for CT imaging, or by the NCRN colorectal nurse if attending the hospital prior to the scheduled CT. This will be done in accordance with the national and local regulatory requirements and will conform to guidelines on Good Clinical Practice. That is, “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”. A copy of the informed consent form is given in Appendix 10.

Consent will be taken in an appropriate environment. The patient will be given the opportunity to have any questions about the study answered. The possible risks and anticipated benefits will be included in the patient information sheet, and explained verbally as part of the consent process.

All Patient Information Sheets & Informed Consent Forms will be version controlled and dated and this information will always be stated in any communication with ethics committees.

Once consent has been obtained the participant should be registered by faxing the ISD Cancer Clinical Trials Team using a fax confirmation sheet:

ISD Cancer Clinical Trials Team Fax no: 0131 275 7512

7.2.2 Emergency settings - proposed action where fully informed consent is not possible

Informed consent will be obtained from all participating patients. The patients will be given the patient information sheet and any questions about the study will be answered by the principal investigator (or delegate). If informed consent cannot be obtained, the patient will not be eligible for the study.

7.2.3. Consent for additional pathological assessment

Informed consent will be obtained from all participating patients for additional pathological assessment of their specimen. Counselling for this will be undertaken by the local hospital team and support services.

7.3 Baseline Assessment

Participants will have vital signs checked, a physical examination and colonoscopy at baseline. A blood sample will also be taken for full blood count, urea and electrolytes, liver function tests, and serum carcinoembryonic antigen (CEA) measurement. The full schedule of procedures is given in Appendix 4

8 Planned intervention

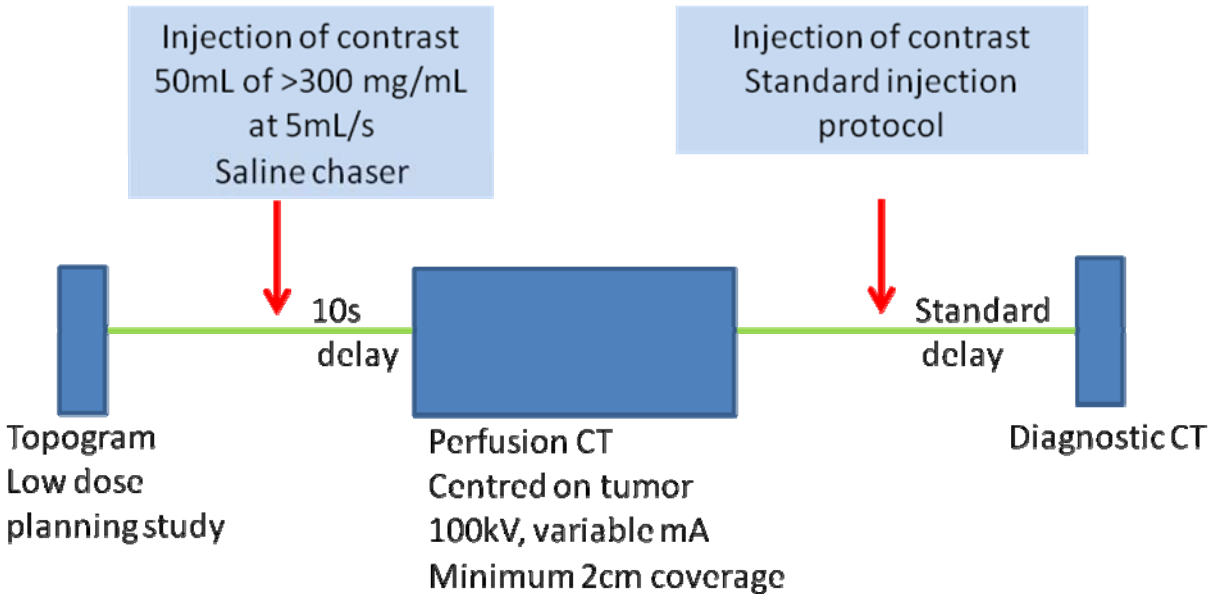
8.1 Imaging & analysis

In addition to standard imaging staging (CT to assess distant spread in all colorectal cancers; pelvic magnetic resonance imaging (MRI) or transrectal ultrasound (TRUS) for locoregional extent in rectal cancer), all eligible consenting patients will undergo an additional Perfusion CT sequence during the standard contrast-enhanced staging CT. This validated additional sequence obtains information over a longer time-span (2 minutes) than conventional CT and provides information regarding tumour perfusion and angiogenesis. To ensure that the technique remains applicable to the NHS, yet up-to-date within the time-period of the study, imaging will be performed on CT scanners with 16 or more detector rows.

The Perfusion CT study will consist of a low-dose limited planning CT (to locate the colorectal cancer) and a dynamic sequence centred on the primary colorectal tumour (a minimum of 2cm z-axis coverage) without table movement after intravenous injection of a standard dose of CT iodinated contrast agent (>300 mg/ml iodine concentration; 50mls injected at 5ml/sec followed with a saline chaser 50mls at 5ml/sec). A tube voltage of 100kV and tube current of 60-200mAs will be used (depending on the CT manufacturer up to a maximum effective dose 20mSv). The dynamic data will be acquired 10 seconds from start of intravenous injection for every 1.5 second for a total of 45 seconds, then every 15 seconds thereafter for an additional 75 seconds

(totaLacquisition time 120 seconds; total number of acquisition time points:30+5=35points). The Perfusion CT sequence will be followed by the standard staging CT acquisition, which will be acquired following a further injection of the standard volume of contrast.

Figure 2 Schema illustrating the scan acquisition protocol



The temporal changes in enhancement will be analysed using commercial software (based on different kinetic models depending on the CT manufacturer: distributed parameter model; Patlak analysis, deconvolution, slope method) to yield the following quantitative parameters: perfusion (blood flow/unit volume), blood volume, permeability surface area product.

The dose constraint (limit) for the additional perfusion CT study has been set at 20mSv to ensure that a good quality Perfusion CT study can be achieved with the different CT scanners at the 10 participating centres.

8.2 Sub studies of test generalisability

The following will be assessed to determine the generalisability of Perfusion CT in a multicentre NHS setting.

- Comparison of measurements obtained on different CT systems. This will be achieved by :

  - Assessment of the difference in Hounsfield Unit measurement between CT systems.
  - Assessment of the linearity of CT enhancement versus iodine concentration across different CT systems: comparison of phantom calibration values for a standard dose of contrast. This will be achieved by phantom measurements at each site (**Section 8.3.1**)
  - Central analysis of data quality (peak signal to noise ratio)
- Comparison of measurements obtained using different kinetic models
  - This will be achieved by central review of all data using the different kinetic models employed in commercial software platforms: distributed parameter analysis, Patlak analysis, deconvolution, & slope method, and assessment of measurement agreement.
- Consistency of measurement at each individual centre
  - This will be achieved by assessment of measurement agreement within and between individual centres and blinded central review of all data using the same commercial software platform. “Clinically acceptable” limits of agreement will be determined a priori by the investigators (with sanction by the DMC), and the limits in practice calculated subsequently, to determine if they lie within this.

8.3 Quality assurance

8.3.1 Site setup - Scan acquisition & phantom studies

Each participating centre will be visited by the research radiographer & physicist to ensure a standardised CT acquisition protocol is inputed directly & checked with dose phantom measurement to ensure this is within the set dose constraint. Noise and resolution of each system will be assessed using standard uniform and line pair phantoms. As the conversion of measurements of tumour enhancement to iodine concentration depends on the linearity of the CT system, further phantom calibrations will be performed to determine this, and a calibration factor will be determined. To resolve any data transfer and other issues at least one test CT will be sent from each centre for central evaluation.

8.3.2 Imaging

All imaging data will be anonymised and sent in DICOM format from each participating centre for central review to ensure image data quality is acceptable and that the study protocol has been adhered to. Data transfer will be carried in accordance with established ethical protocols: all patient identifiers will be removed prior to transfer and coded. The code will be held securely by the local PI at each site.

8.3.3 Image analysis: Perfusion CT

All Perfusion CT scans will be analysed at each of the participating institutions by a radiologist according to a pre-agreed standardised protocol (**Appendix 2**), applied and validated in our previous colorectal cancer studies, as the study aims to test the technique's applicability in a multicentre setting. All participants of the study will be trained by an experienced Perfusion CT user to use the Perfusion CT software using test datasets of primary colorectal cancers. All Perfusion CTs will be reviewed centrally by an experienced Perfusion CT user. Any significant differences between results of local and central analysis (>30% difference in values i.e. > usual tumour variation) will be highlighted and discussed to ensure protocol was adhered to.

8.3.4 Surveillance CTs

All the yearly surveillance CTs (and any symptomatic CTs performed at an earlier time due to suspicion of metastases) will be reviewed centrally to confirm whether metastases are present/absent.

9 Planned treatment and follow up

The patient will undergo planned tumour management following imaging staging as per local policy decided at MDT (guided by NICE recommendations; 30). This may involve (a) curative primary tumor resection; +/- neoadjuvant chemoradiation; +/- adjuvant chemotherapy +/- metastectomy; or (b) palliative treatment only, if widespread metastatic disease is present or if co-morbidity precludes surgery.

All patients undergoing curative treatment will be followed up for 36 months, which is standard practice for all participating centres. This includes 6-monthly clinic visits including clinical examination, standard blood tests (including full blood count, urea and electrolytes, liver function tests, and serum carcinoembryonic antigen (CEA) measurement) and yearly standard contrast enhanced CT of the chest, abdomen and pelvis. This is standard practice for each of the participating centres. A colonoscopy at year 3 is optional according to local practice. A schedule of procedures for patient visits is included in Appendix 4.

When disease relapse is detected, this will be confirmed either through histology or collaborative/follow up imaging as per standard practice for the institution. Patients who do not undergo curative treatment will not take further part in the study. Follow up data will be recorded yearly using the case report form (CRF) including information of treatment, mode of follow up, date of relapse, confirmation of metastases and date of death (where present). This will be

performed for each patient by the local PI (or delegate) and sent to the clinical trials unit for inclusion in the database.

At a fixed calendar date 60 months after the last patient is scanned, death data will be sought from the NHS Information Centre Medical Research Information Service (MRIS). An application for this data will be made to the NHS Information Centre MRIS, or the organization that takes responsibility for those processes at the time of collection.

10 Reference standard

The reference standard for the primary diagnosis of colorectal cancer will be histological analysis of the surgical specimen. Central review of all specimens will be performed at University College Hospital, London. Reporting will be performed using a standardized reporting sheet (Appendix 3).

10.1 Pathological staging

As per standard practice, the following will be assessed:

1. Local invasion (T stage); including tumour extension in mm from the muscularis propria
2. Nodal invasion (N stage)
3. Tumour size
4. Extramural venous invasion
5. Involvement of the resection margin
6. Presence/absence of background abnormalities

Assessment of the prognostic value of the following will be considered in addition:

1) The circumferential resection margin, measured in mm, from the tumour edge to the nearest dissected margin of the resection specimen
2) Tumour regression grade following neoadjuvant therapy

Additional staining for K-RAS mutation status, microsatellite instability; and markers of angiogenesis CD105, VEGF, Glut-1, will be undertaken centrally.

Pathological parameters T stage and N stage are included as individual variables in the model. Other pathology parameters will be evaluated as a composite score or in simple combinations to assess the added value of including these additional pathology measures in the best prognostic model developed within this grant, to predict development of metastasis.

10.2 Disease relapse

Categorization of patients with and without subsequent recurrence will be via (a) histology of metastases, or (b) imaging and clinical course, in those patients who are too ill to continue therapy or who refuse further investigation. The definition for the end of the time period for disease free survival will be based on details in Appendix 5.

11 Statistical considerations

11.1 Proposed Sample size

With at least 10 centres each recruiting at 3 patients/month (up to 50% of eligible patients; this recruitment rate was achieved in the previous pilot study [24]) over a period of 12 to 15 months, it is estimated this prospective cohort study can recruit 370 patients with a median follow up of 40 months. We estimate that 30% of patients will progress to metastasis, with most events occurring within 36 months [31]. This gives an effective sample size of approximately 80 patients with the primary outcome uncensored time to metastasis (taking into account patients with metastases at staging (up to 20%) who will cease to participate). A second outcome of time to death from any cause will be collected. Based on a reclassification index similar to Pencina et al [32] of patients as high risk for metastasis (top 30%) compared between the two models, 300 patients with 80 events would have 80% power to detect a 15% difference in correct risk classifications [33], with allowance for loss to follow-up (estimated at <10% from previous pilot study experience [24]).

We used the pilot study results as an estimate of the likely correlation between the current method and results from a prognostic model including CT perfusion measurements.

		Current Method (Method 2)		TOTAL
New method (method 1)		Correct prediction (compared to reference standard)	Wrong prediction (compared to reference standard)	
	Correct prediction (TP and TN patients by reference standard)	0.56	0.26	0.82
	Wrong prediction (FP and FN patients by reference standard)	0.09	0.09	0.18
	TOTAL	0.65	0.35	1.00

The study will be based on 2-sided 95% level of significance.

The proposed sample size of 80 events for a model with 8 candidate variables also meets the usual 'rule of thumb' of >10 events per candidate variable for developing a stable prognostic model [41].

11.2 Analysis plan for primary outcome

The study endpoint will be a fixed calender date. Analysis of data for patients will use a fixed time period of 36 months follow up for each individual patient, and 60 months follow up for each individual patient for 5-year death data collection.

We will develop a prognostic model using measurements from Perfusion CT with the prognostic variables: N stage, T stage, age, tumour size, organ, treatment and macroscopic vascular invasion. The primary model will be disease free survival defined as: all deaths, distant metastasis, second primary but excluding locoregional recurrence. A secondary model will use overall survival.

Although we will present standard measures of prognostic model performance such as discrimination and calibration, we favour assessing model performance using improvement in the correct predictions for individual patients [32].

We will assess model performance, based on the change in the number of patients with a correct or incorrect prognosis of metastasis, by comparing model predictions to current clinical practice (High risk = Duke's C patients and Duke's B if <50 yrs or pathology report includes extramural invasion or patient has a clinical obstruction.) We will use two outcome metrics to enable the consequences of extra true positive predictions and extra false positive predictions to be analysed separately, as these may have different clinical consequences. These measures will be (i) the change in sensitivity (due to the use the primary outcome model using CT perfusion parameters) multiplied by the disease prevalence, and (ii) the change in the specificity multiplied by (1-prevalence). Information from secondary outcome #7 will be used to provide sensitivity analyses for patient and clinician weightings of measures (i) and (ii) to facilitate an overall assessment of model performance.

We will use a Cox model of disease free survival and display Kaplan Meier plots for three risk groups (high risk, medium risk and low risk). Information from secondary outcome #7 will be used to inform a threshold for medium risk versus low risk patients. Missing data will be imputed

using methods based on Vergouwe [34], Jannsen [35] and Marshall [36]. (The model will be adjusted for clustering of patients within centres using methods based on Vaida [37].

From analysis of our prior pilot data we found several CT parameters are correlated, so we will develop a summary score using principal components analysis before model development. We will use Perfusion CT parameter measurements from individual centres with central review measurements for models used in secondary outcomes #5 and #6. Continuous variables will be retained wherever possible to retain statistical power in the model [38]. Analysis of the pilot study data (35 patients and 8 metastases) using this method showed an improvement in the number of correct patient diagnoses. If such a result had been seen in a large number of patients, it would suggest Perfusion CT parameters could have potential to be valuable for prediction of metastasis. We will also compare: the performance of best prognostic models developed with and without Perfusion CT parameters; models using Perfusion CT parameters from individual centres versus central review; prognostic models using overall survival as outcome. Substudies will assess generalisability of measurement of Perfusion CT parameters by the agreement of observers and machines/software. These studies will use Bland-Altman methods for limits of agreement [39].

Summary table of analyses for primary and secondary outcomes

		Methods compared in outcome	
Outcome	**Summary**	**Method 1**	**Method 2**
Primary outcome	Best model including CT perfusion compared to current method	Prognostic model for DFS, including standard variables and CT perfusion	Current clinical practice
Secondary outcome #1	Best model with standard variables compared to current method	Prognostic model for DFS with standard variables only (no CT perfusion variables)	Current clinical practice
Secondary outcome #2	Added value of CT perfusion measurements in prognostic model	Prognostic model including standard variables and CT perfusion • DFS • OS	Prognostic model with standard variables only (no CT perfusion variables) • DFS • OS
Secondary outcome #3	Added value of alternative scores for CT perfusion parameters	Composite single score of five parameters in prognostic mode	Simpler scores for CT perfusion parameters (e.g. single or pairs of parameters)
Secondary outcome #4	Added value of pathology variables in prognostic model	Preferred prognostic model from study with pathology variables as a single score	Preferred prognostic model from study without prognostic variables
Secondary outcome #5	Comparison of CT perfusion measurements and variability	Hospital measurements	Central review measurements

Secondary outcome #6	Added value of CT perfusion, based on central review data	Prognostic model including standard variables and CT perfusion from central review data • DFS • OS	Prognostic model with standard variables only (no CT perfusion variables) • DFS • OS
Secondary outcome #7	Different relative weightings for value of extra patients diagnosed with true positive or false positive results	Comparison of model performances at different relative clinical weightings • use in primary outcome and secondary outcome #1	
Secondary outcome #8	Model at 60 month time period instead of 36 months used in other models	Best prognostic model based on parameters for DFS, but using 60 month overall survival	Current clinical practice
Secondary outcome #9	Exploratory biology study investigating potential relationships between CT perfusion parameters and pathology characteristics in the tumours.	Comparisons based on tumour characteristics and not prognostic models	

11.3 Evaluation strategy

Internal validation using bootstrap analysis will be used to correct for overfitting and over optimism in our prognostic model and final rule, which results from using the same patients to develop and evaluate a model. Corrections using "shrinkage" will be based on 200 bootstrap samples to provide: (a) averaged values of coefficients which will be used in the final rule, and (b) averaged estimates of the change in sensitivity and change in specificity; (c) discrimination and calibration at 3 year survival [40]

12 Reporting & monitoring procedures

12.1 Data reporting and monitoring

Data from Perfusion CT analysis and Case Report Forms will be entered onto a central database with extensive data validation checks alerting all missing data to be queried. Missing data will be monitored and strategies developed & employed to minimise its occurrence. Central statistical data monitoring will summarise missing or inconsistent data periodically. As part of quality assurance at ISD Cancer Clinical Trials Team 10% of paper case report forms are checked against the database.

12.2 Site monitoring & risk assessment

Each site will be visited in the first year by the CTU and Chief Investigator; risk assessments will be performed at 6-12 months after queries, staff changes, or a new site going online. Checks will be performed of the following: consent forms (100%), eligibility (10%), primary and secondary endpoint data (randomly selected; 10%).

12.3 Data protection

All data will be handled, computerised and stored in accordance with the Data Protection Act 1998 and NHS National Services Scotland Confidentiality Guidelines.

12.3.1 Data Collection

Data generated will be collected by the ISD Cancer Clinical Trials Team, who will be responsible for checking the data, entering it on the trial database and validating it. The data collected will include:

- initial clinical details at randomisation
- adverse events
- survival/ recurrence details

12.3.2 Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number (Community Health Index and/or hospital number in Scotland) will be collected to enable tracing through national records. The personal data recorded on all records will be regarded as confidential, and to preserve each patient's anonymity, only their initials and date of birth will be recorded on CRFs. The patients will be identified within the CRFs by the use of a unique trial number allocated to them upon entry into the study.

The Principal Investigator (or delegate) at each site must keep a log of patients' trial numbers, names, addresses and hospital numbers. The Principal Investigator must ensure that patient confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

ISD Cancer Clinical Trials Team will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Patients will only be referred to by Trial Number, Initials and Date of Birth in any essential trial related correspondence, including Case Report Forms and Serious Adverse Reaction Reports.

All patient identifiable data will be handled, computerised and stored in accordance with the Data Protection Act 1998 and NHS National Services Scotland Confidentiality Guidelines.

12.4 Proposed time period for retention of relevant trial documentation.

The investigator at each investigational site must make arrangements to store the essential study documents, including the Investigator Site File, until the clinical trials unit informs the investigator that the documents are no longer to be retained, or for a maximum of 15 years, whichever is soonest. ISD Cancer Clinical Trials Team undertakes to store originally completed Case Report Forms and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the PI.

12.5 Adverse event reporting

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence in a patient which does not necessarily have a causal relationship with the study treatments or procedures. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with a treatment or procedure, whether or not considered related.

Adverse Reaction (AR): All noxious and unintended responses related to a study treatment or procedure should be considered adverse drug reactions.

Serious Adverse Event (SAE): Any untoward medical occurrence in a patient that

a) Results in death
b) Is life-threatening
c) Requires hospitalisation or prolongation of existing hospitalisation
d) Results in persistent or significant disability or incapacity
e) Consists of a congenital anomaly or birth defect
f) Is otherwise considered to be medically significant by the investigator (e.g. intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation).

The term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisations planned prior to enrolment in the trial or for social reasons should not normally be considered as SAEs unless the hospitalisation has to be prolonged. Treatment in an emergency room of less than 24 hours or on an out-patient basis that does not meet any other serious criteria should not be considered as an SAE.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that is classified as serious and it is suspected that it is caused by a study treatment or procedure. The nature, severity or outcome of this adverse reaction also must not be consistent with the Investigator's Brochure (IB) or Summary of Product Characteristics for the treatment or procedure.

Recording of Adverse Events

All adverse events (serious and non-serious) occurring after the signing of informed consent through to 30 days after the study procedure will be recorded in the subject's notes and transcribed to the CRF.

Any medical conditions or diseases present prior to signing of informed consent should only be considered an adverse event if there is a worsening of the condition.

All serious adverse events considered by the investigator to be related to the study procedure / treatment (SARs) should be notified to ISD Cancer Clinical Trials Team within 24 hours using the Serious Adverse Reaction form.

A list of adverse events /reactions that are **expected** in patients receiving CT contrast agent and Buscopan are given in Appendix 11.

Recording and Reporting of Serious Adverse Reactions (SARs)

Contact Details for Reporting SARs

ISD CCTT Fax:	+44 131 275 7512 (preferred method)
ISD CCTT Telephone:	+44 131 275 7276/ 4278 (Mon – Fri 9am-5pm)

The SAR report form must be signed by the Principal Investigator of the centre involved and faxed to ISD Cancer Clinical Trials Team within 24 hours of first becoming aware of the event. All initial SAR reports should contain the following minimum information:

- Reporter information
- At least one subject identifier (trial number/patient initials)
- Event term
- Assessment of relatedness
- Serious criteria

A fax receipt will be sent to the relevant centre by ISD Cancer Clinical Trials Team to acknowledge receipt of the SAR report form, and ISD will notify the Chief Investigator (CI).

All SARs will be forwarded to the CI by ISD Cancer Clinical Trials Team for assessment of expectedness. Any SAR that is deemed to be unexpected (i.e. a SUSAR) will be notified to the appropriate Research Ethics Committees within 15 days of becoming aware of the event.

ISD Cancer Clinical Trials Team will then notify the CI and the PI's at all of the participating centres of the occurrence of all SUSARs.

12.6 Pregnancies

Any pregnancy in a trial participant or their partner that occurs within 60 days post study procedure, should be reported to ISD Cancer Clinical Trials Team within 24 hours of becoming aware of its occurrence, using the contact details above. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary abortion, details of birth and presence or absence of any birth defects, congenital abnormalities or maternal or newborn complications. Any birth defects or congenital abnormalities must be reported as SAEs.

13 Research Governance

13.1 Study Organisation

The study sponsor will be King's College London. The study will be managed by ISD Cancer Clinical Trials Team, based in Edinburgh, on behalf of Dr Vicky Goh (Chief Investigator). Central imaging review will take place at Mount Vernon Hospital, Northwood, London. Central histopathology review will take place at University College Hospital, London. Completed Case Report Forms should be returned to ISD Cancer Clinical Trials Team for inclusion in the study database.

13.1.2 Chief Investigator – The Chief Investigator will have overall responsibility for the design, co-ordination and management of the study. These include:

- Trial authorization including responsibility for the protocol and obtaining approvals
- Ensuring the trial is conducted according to Good Clinical Practice
- Assessment of SAEs and providing a prompt response as to whether a SAE is a SUSAR

13.1.3 Clinical Trials Unit – The Chief Investigator has delegated the responsibility for overall project management, data management and monitoring to ISD Cancer Clinical Trials Team. Responsibilities include:

- Assistance with completion of the IRAS form and MREC communication
- Production of trial specific documentation (ie CRFs)
- Assistance with SSA procedures within centres
- Facilitating set up of trial centres
- Data management
- Monitoring
- Pharmacovigilance – Reporting of SARs / SUSARs

13.1.4 Statistical Analysis – Dr Susan Mallett, at the CR-UK Centre for Statistics in Medicine, Oxford will undertake the final analysis arising for this study.

13.1.5 Imaging Data Analysis – Guys and St Thomas, London will be responsible for extracting, analyzing and reporting imaging data

13.1.6 Histopathology Review - University College Hospital, London will be responsible for reviewing and reporting on pathological specimens

13.1.7 Local Project Teams – These will consist of Surgeons and/or Oncologists (responsible for introducing the patient to the study and ensuring eligibility and consent), Research Nurse (responsible for patient recruitment, obtaining consent and co-ordination of all aspects of data collection), Radiologists and Radiographers (responsible for completing Perfusion CT scans to protocol). Centres are specifically responsible for conducting the trial in accordance with the protocol, Standard Operating Procedures (SOPs), the trial agreement and Good Clinical Practice.

13.1.8 Trial Steering Committee and Data Monitoring Committee

King's College London will act as study sponsor. Central study co-ordination, data collection, monitoring and organisation of the data for the statistical analyses will be undertaken by ISD Cancer Clinical Trials Team, which has processes in place to ensure that the study will not open to recruitment until appropriate approvals and authorisations have been obtained from the independent research ethics committee, and NHS Research and Development departments. The trial steering committee (TSC), including members of the research team and an independent radiologist, oncologist, statistician, and lay member, will be responsible for the progress and conduct of the study and convene twice yearly. A data monitoring committee (DMC) will convene at yearly intervals to review all data including adverse events and develop a stopping policy for the trial, if necessary. This will be run as per DAMOCLES.

14 FINANCING AND INSURANCE

This study is an investigator-led trial endorsed by the National Institute for Health Research Health and Technology Assessment programme. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

15 PUBLICATION POLICY

All presentations and publications relating to the trial must be authorized by the Trial Management Group. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by the Trial Management Group, representatives from ISD Cancer Clinical Trials Team and high accruing clinicians. The trials offices and all participating centres and clinicians will be acknowledged in this publication. Any data that might detrimentally affect the progress of the trial will not be released prior to the end of the trial. No investigator may present or attempt to publish data concerning their patients, which is directly relevant to the questions posed in the trial, until the main results have been published.

References

1. Cancer Research UK, Cancer Stats, Incidence – UK, 2009
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al.: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001, 345:638-646.
3. Buyse M, Burzykowski T, Carroll K, Michiels S, Sargent DJ, Miller LL, Elfring GL, Pignon JP, Pascal Piedbois P. Progression-Free Survival Is a Surrogate for Survival in Advanced Colorectal Cancer. J Clin Oncol 2007;25(33):5218-24.
4. IMPACT investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet 1995; 345(8995):939-44.
5. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, De Gramont A: Multicenter International Study of Oxaliplatin/5-flurouracil/leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC): Oxaliplatin, flurouracil and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.
6. Andre T, Sargent D, Tabernero J, O'Connell M, Buyse M, Sobrero A, Misset JL, Boni C, de Gramont A. Current issues in adjuvant treatment of stage II colon cancer. Ann Surg Oncol 2006;13:887-98.
7. Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, Jones J, Rockette H. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B vs. Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, C-04) J Clin Oncol 1999;17:1349-55.
8. MERCURY study group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006;333:779
9. Smith NJ, Bees N, Barbachano Y, Norman AR, Swift RI, Brown G. Preoperative computed tomography staging of nonmetastatic colon cancer predicts outcome: implications for clinical trials. Br J Cancer 2007;96:1030-6
10. Burton S, Brown G, Bees N, Norman A, Biedrzycki O, Arnaout A, Abulafi AM, Swift RI. Accuracy of CT prediction of poor prognostic features in colonic cancer. Br J Radiol 2008;81:10-19
11. Cenic A, Nabavi DG, Craen RA, Gelb AW, Lee TY. Dynamic CT measurement of cerebral blood flow: a validation study. Am J Neuroradiol 1999;20:63-73.
12. Cenic A, Nabavi DG, Craen RA, Gelb AW, Lee TY. A CT method to measure hemodynamics in brain tumors: validation and application of cerebral flow maps. Am J Neuroradiol 2000;21:462-70.

13. Purdie TG, Henderson E, Lee TY. Functional CT imaging of angiogenesis in rabbit VX2 soft-tissue tumor. Phys Med Biol 2001;46:3161-3175
14. Pollard RE, Garcia TC, Stieger SM, Ferrara KW, Sadlowski AR, Wisner ER. Quantitative evaluation of perfusion and permeability of peripheral tumors using contrast enhanced computed tomography. Invest Radiol 2004; 39:340-9.
15. Yi CA, Lee KS, Kim EA, Han J, Kim H, Kwon OJ, Jeong YJ, Kim S. Solitary pulmonary nodules: dynamic enhanced multidetector row CT study and comparison with vascular endothelial growth factor and microvessel density. Radiology 2004;233: 191-9.
16. Tateishi U, Kusumoto M, Nishihara H, Nagashima K, Morikawa T, Moriyama N. Contrast enhanced dynamic computed tomography for the evaluation of angiogenesis in patients with lung carcinoma. Cancer 2002;95: 835-842.
17. Goh V, Halligan S, Daley F, Guenther T, Wellsted D, Bartram CI. Assessment of colorectal cancer vascularity: Quantitative assessment with MDCT - Do tumor perfusion measurements reflect angiogenesis? Radiology 2008; 249: 510-517.
18. Goh V, Padhani AR, Rasheed S. Functional imaging of colorectal cancer angiogenesis. Lancet Oncology 2007;8:245-55.
19. Meijerink MR, Van Cruijsen H, Hoekman K, Kater M, Van Schaik C, Van Waesberghe JH, Giaccone G, Manoliu RA. The use of perfusion CT for the evaluation of therapy combining AZD2171 with gefitinib in cancer patients. Eur Radiol 2007;17: 1700-13.
20. Ng QS, Goh V, Milner J, Stratford MR, Folkes LK, Tozer GM, Saunders MI, Hoskin PJ. Effect of nitric-oxide synthesis on tumour blood volume and vascular activity: a phase I study. Lancet Oncol 2007; 8: 111-8.
21. Ng QS, Goh V, Carnell D, Meer K, Padhani AR, Saunders MI, Hoskin PJ. Tumor antivascular effects of radiotherapy combined with combretastatin a4 phosphate in human non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2007; 67:1375-80.
22. Koukourakis MI, Mavanis I, Kouklakis G, Pitiakoudis M, Minopoulos G, Manolas C, Simopoulos C. Early anti-vascular effects of bevacizumab anti-VEGF monoclonal antibody on colorectal carcinomas assessed with functional CT imaging. Am J Clin Oncol 2007; 30:315-8.
23. Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DT, Hartford AC, Fischman AJ, Clark JW, Ryan DP, Zhu AX, Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY, Jain RK. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 2004;10: 145-7.

24. Goh V, Halligan S, Wellsted D, Bartram CI. Can perfusion CT assessment of primary colorectal adenocarcinoma blood flow at staging predict for subsequent metastatic disease? – Pilot Study. European Radiology 2009; 19: 79-89.
25. Hermans R, Meijerink M, Van den Bogaert W, Rijnders A, Weltens C, Lambin P. Tumor perfusion rate determined non-invasively by dynamic computed tomography predicts outcome in head-and-neck cancer after radiotherapy. Int J Radiat Oncol Biol Phys 2003;57:1351-6.
26. Haider MA, Milosevic M, Fyles A, Sitartchouk I, Yeung I, Henderson E, Lockwood G, Lee TY, Roberts TP. Assessment of the tumor microenvironment in cervix cancer using dynamic contrast enhanced CT, interstitial fluid pressure and oxygen measurements. Int J Radiat Oncol Biol Phys 2005;62:1100-7.
27. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ. 2009 May 28;338:b605.
28. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ. 2009 Jun 4; 338:b606.
29. Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000; 53:219-221.
30. Improving outcomes in colorectal cancer. NICE guidance, 2004.
31. Sargent DJ, Patiyil S, Yothers G, Haller DG, Gray R, Benedetti J, Buyse M, Labianca R, Seitz JF, O'Callaghan CJ, Francini G, Grothey A, O'Connell M, Catalano PJ, Kerr D, Green E, Wieand HS, Goldberg RM, de Gramont A; ACCENT Group. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. J Clin Oncol 2007;25:4569-74
32. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72.
33. Julious SA, Campbell MJ, Altman DG. Estimating sample sizes for continuous, binary, and ordinal outcomes in paired comparisons: practical hints.J Biopharm Stat 1999;9:241-51.
34. Vergouwe Y, Royston P, Moons KG, Altman DG. Development and valdation of a prediction model with missing predictor data: a practical approach. J Clin Epidemiol 2010; 63: 205-14.

35. Janssen KJM, Vergouwe Y, Donders RT, Harrell FE, Chen Q, Grobbee DE, Moons KG. Dealing with missing predictor values when applying clinical prediction models. Clin Chem 2009; 55: 994-1001,
36. Marshall A, Altman DG, Royston P, Holder RL. Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study. BMC Med Res Methodol 2010; 10:7
37. Vaida F, Xu R. Proportional hazards model with random effects. Stat Med 2000;19:3309-24.
38. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea.Stat Med 2006;25:127-41.
39. Bland M, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:
307-10
40. van Houwelingen JC, le Cessie S.Predictive value of statistical models. Stat Med.1990;9(11):1303-1325.
41. Harrell FE, Jr., Lee KL, Califf RM, Pryor DB, Rosati RA: Regression modelling strategies for improved prognostic prediction. *Stat Med* 1984, 3:143-152.

Appendix 1. Scan acquisition and reconstruction parameters

Sequence	Topogram	Low dose planning sequence	Dynamic acquisition
Siemens	Spiral	Spiral	Dynserio 7.2
kV	120	100	100
mA BMI <30	36	130 with tube current modulation	130 without tube current modulation
mA BMI >30	36	150 with tube current modulation	150 without tube current modulation
Rotation time	-	0.5s	0.5s
Detector configuration	-	24X1.2mm	24X1.2mm
Slice collimation	0.6mm	5mm	7.2mm
Temporal interval /Length of scan	Topogram length 256mm-	Pitch 1.2 Direction craniocaudal	Cycle time 1.5/15seconds/120seconds
Reconstructed FOV		380mm	380 mm
Reconstruction kernel	-	B30f medium smooth	B30f medium smooth
Reconstruction slice thickness	-	5mm	7.2mm (<64MDCT) 5 mm (>64 MDCT)
GE	Spiral	Spiral	Axial mode
kV	120	100	100
mA BMI <30	30	80 with tube current modulation	80 without tube current modulation
mA BMI >30	30	100 with tube current modulation	100 without tube current modulation
Rotation time		0.5s	0.5s
Detector configuration			4*5mm 8*5mm
Slice collimation	0.6mm	5mm	5mm
Temporal interval /Length of scan	Topogram length 256mm-	Pitch 1.2 Direction craniocaudal	Cycle time 1.5/15 seconds/120seconds
Reconstruction kernel		B30 soft	B30 soft
Reconstruction slice thickness		2.5mm 5mm	2.5mm 5mm
Toshiba			
kV		100	100
mA		100	100
Rotation time		0.5s	0.5s
Detector configuration		320*0.5	320*0.5
Slice collimation		0.5mm	0.5mm
Temporal interval /Length of scan			Cycle time 1.5/15 seconds/120seconds
Reconstruction kernel		B30 soft	B30 soft
Reconstruction slice thickness		5mm	5mm

Appendix 2

Proforma for reporting Perfusion CT

Centre **Patient identifier**

Date of birth: **Sex** **Male** **Female**

Tumour morphology:

Tumour site: Rectum Sigmoid DC TC AC Caecum

Tumour size: cm

TNM stage: **Clinical stage**: Stage I II III IV

Perfusion CT:

Threshold value: -50 to 150HU

Image slice exclusion: No Yes: Which images?

Motion correction: No Yes

Placement of end of first pass (GE): image number time

Reconstructed slice thickness: 5mm 7.2mm

Recorded parameter values:
Cranial to caudal for all slices in which the tumour is visible

	BF	BV	PS	MTT	ROI size
Slice 1					
Slice 2					
Slice 3					
Slice 4					
Slice 5					
Slice 6					
Slice 7					
Slice 8					
Slice 9					
Slice 10					
Slice 11					
Slice 12					
Slice 13					
Slice 14					
Slice 15					

Appendix 3

Standardized reporting proforma for pathological specimens

Patient trial number:_____ Sex (please tick): M☐ F☐

Initials: _____ Hospital: _____

Specimen type: Total colectomy / Right hemicolectomy / Left hemicolectomy / Sigmoid colectomy / Anterior resection / Abdominoperineal excision / Other (state) .....

Gross description

Site of tumour .....
Maximum tumour diameter: .....mm
Distance of tumour to nearer cut end .....mm
Tumour perforation (pT4) Yes ☐ No ☐
If yes, perforation is serosal ☐ retro/infra peritoneal ☐
For rectal tumours:
Relation of tumour to peritoneal reflection (tick one):
Above ☐ Astride ☐ Below ☐
Plane of surgical excision (tick one):
Mesorectal fascia ☐
Intramesorectal ☐
Muscularis propria ☐
For abdominoperineal resection specimens:
Distance of tumour from dentate line .....mm

Histology

Type
Adenocarcinoma Yes ☐ No ☐

If No, other type .....

Differentiation by predominant area
Well / moderate ☐ Poor ☐

Local invasion
No carcinoma identified (pT0) ☐
Submucosa (pT1) ☐
Muscularis propria (pT2) ☐
Beyond muscularis propria (pT3) ☐
Tumour invades adjacent organs (pT4a) ☐
AND/OR
Tumour cells have breached the serosa (pT4b) ☐
Maximum distance of spread beyond muscularis propria .....mm

Response to neoadjuvant therapy
Neoadjuvant therapy given Yes ☐ No ☐ NK ☐
If yes:
No residual tumour cells / mucus lakes only ☐
Minimal residual tumour ☐
No marked regression ☐

Tumour involvement of margins

	N/A	Yes	No
Doughnuts	☐	☐	☐
Margin (cut end)	☐	☐	☐
Non-peritonealised 'circumferential' margin	☐	☐	☐

Histological measurement from tumour to non-peritonealised margin ..... mm

Metastatic spread

No of lymph nodes present .....
No of involved lymph nodes .....
(pN1 1–3 nodes, pN2 4+ nodes involved)
Highest node involved (Dukes C2) Yes ☐ No ☐
Extramural venous invasion Yes ☐ No ☐
Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: .....

Background abnormalities: Yes ☐ No ☐

If yes, type: (delete as appropriate)

Adenoma(s) (state number .....)
Familial adenomatous polyposis / Ulcerative colitis / Crohn's disease / Diverticulosis / Synchronous carcinoma(s)
(complete a separate form for each cancer)

Other ....

Pathological staging

Complete resection at all surgical margins
Yes (R0) ☐ No (R1 or R2) ☐

TNM (5th edition)

(y) pT ..... (y) pN .....(y) pM .....

Dukes
Dukes A ☐ (Tumour limited to wall, nodes negative)
Dukes B ☐ (Tumour beyond M. propria, nodes negative)
Dukes C1 ☐ (Nodes positive and apical node negative)
Dukes C2 ☐ (Apical node involved)

Signature: ..... Date ...../...../..... SNOMED Codes T..... / M.....

Appendix 4: Schedule of procedures

A minimum follow up schedule will be standard at all centres. This will include

- yearly CT (chest, abdomen and pelvis) at years 1, 2 and 3
- two yearly clinic visits in years 1 and 2

* Baseline assessment, baseline CT perfusion and CT baseline staging tests will aim to take place on same patient visit

Procedure	Baseline Assessment*	Baseline perfusion CT*	Baseline staging CT*	Rectal cancers: MRI &/or TRUS	Surgery	Year 1: Clinic visit 1 (3-6 months)	Year 1: Clinic visit 2 (6-12 months)	Year 1 CT scan (chest, abdomen & pelvis)	Year 2: Clinic visit 1 (15-18 months)	Year 2: Clinic visit 2 (18-24 months)	Year 2 CT scan (chest, abdomen & pelvis)	Year 3: Clinic visits (24-36 months)	Year 3 CT scan (chest, abdomen & pelvis)
Informed consent	X												
Demographics	X												
Eligibility check	X												
Vital signs	X					X	X		X	X		X	
Blood sample including CEA	X					X	X		X	X		X	
Physical examination	X					X	X		X	X		X	
Medical history	X					X	X		X	X		X	
Colonoscopy	X											X (optional)	
Assessment of need for FU imaging & tests						X	X	X	X	X	X	X	X
Baseline staging CT scan			X										
CT perfusion measurements		X											
Imaging to plan rectal surgery				X									
CT scan: Assessment for tumour recurrence								X			X		X
CT scan: Assessment for second primary cancers								X			X		X
Pathology					X								
Adverse event update		X											

Appendix 5: Definitions for end of time period for disease free survival outcome(DFS)

The start of the DFS time period will be date of baseline CT staging.

Situation	Date	Outcome
End of year CT scan shows metastasis	Date of first scan showing recurrence	recurrence
Chest X ray abnormal, clinic visit, multiple imaging, some showing metastasis (i) CT scan - scheduled or unscheduled (ii) no CT scan	(i) date of CT scan (ii) date of subsequent clinic visit where decision made on basis of recurrence event	(i) recurrence (ii) recurrence
Clinical suspicion (e.g. CEA raised) but no FU imaging and no CT scan (i) hospital visit (ii) GP visit only (likely only very elderly patients, who are unable to attend hospital)	(i) date of subsequent clinic visit where decision made on basis of recurrence (ii) GP - individual patient GP follow up would be difficult and laborious	(i) recurrence (ii) recurrence censored at last scan* (ii) death from ONS
Loss to follow up or patient withdraws consent	(i) date of last CT scan or baseline	(i) censored recurrence (i) death from ONS
Clinical suspicion but patient too ill to attend any tests, no CT scan (i) hospital visit (ii) GP visit only	(i) date of clinic visit or inpatient admission when decision made that patient is too ill to attend for CT (ii) hospice admission? GP visit	(i) censored recurrence (i) death from ONS (ii) censored recurrence (ii) death from ONS

* this censoring may be informative: we are hoping numbers are low and would not affect study results. A sensitivity analysis could be done to include these patients, but it would require follow up with individual patient GP

Appendix 6. Project timetable and milestones

Expected start date: August 2010

Months 0 – 6; Study set-up

Steering committee to finalise protocols: Perfusion CT acquisition, analysis, quality assurance, data analysis; Development of statistical prognostic model; Confirmation of participating institutions; Establishment of (sub)contracts with participating institutions; Application to the participating centres' Research and Development departments; Application for Multi-centre Research Ethics Committee via IRAS and coordination of submission of site specific assessments; Appointment of research staff; Purchase of necessary equipment; Produce investigator packs for centres; produce case reports forms & develop CRF based database; Site initiation: Set up & quality assurance of Perfusion CT protocol; On-site training in Perfusion CT.

Month 7; Commence recruitment.

Consent of first patient; Target recruitment rate of 30 patients per month.

Months 7-21; Recruitment

Monitoring of recruitment rates by trial co-ordinator and statistician, identification of problems & need to open up further sites to reach target accrual; Target (370 patients) achieved by month 21; Analysis of Perfusion CT studies at participating sites

Month 12-36; Central review/analysis of all Perfusion CT data; Substudies performed

Assessment of data; Substudies performed; manuscript preparation & submission

Month 21-54; Follow-up

Collection of data for final patients recruited; Central review of surveillance CT to confirm/exclude metastases; Data cleaning in anticipation of data base closure

Months 54-60; Analysis

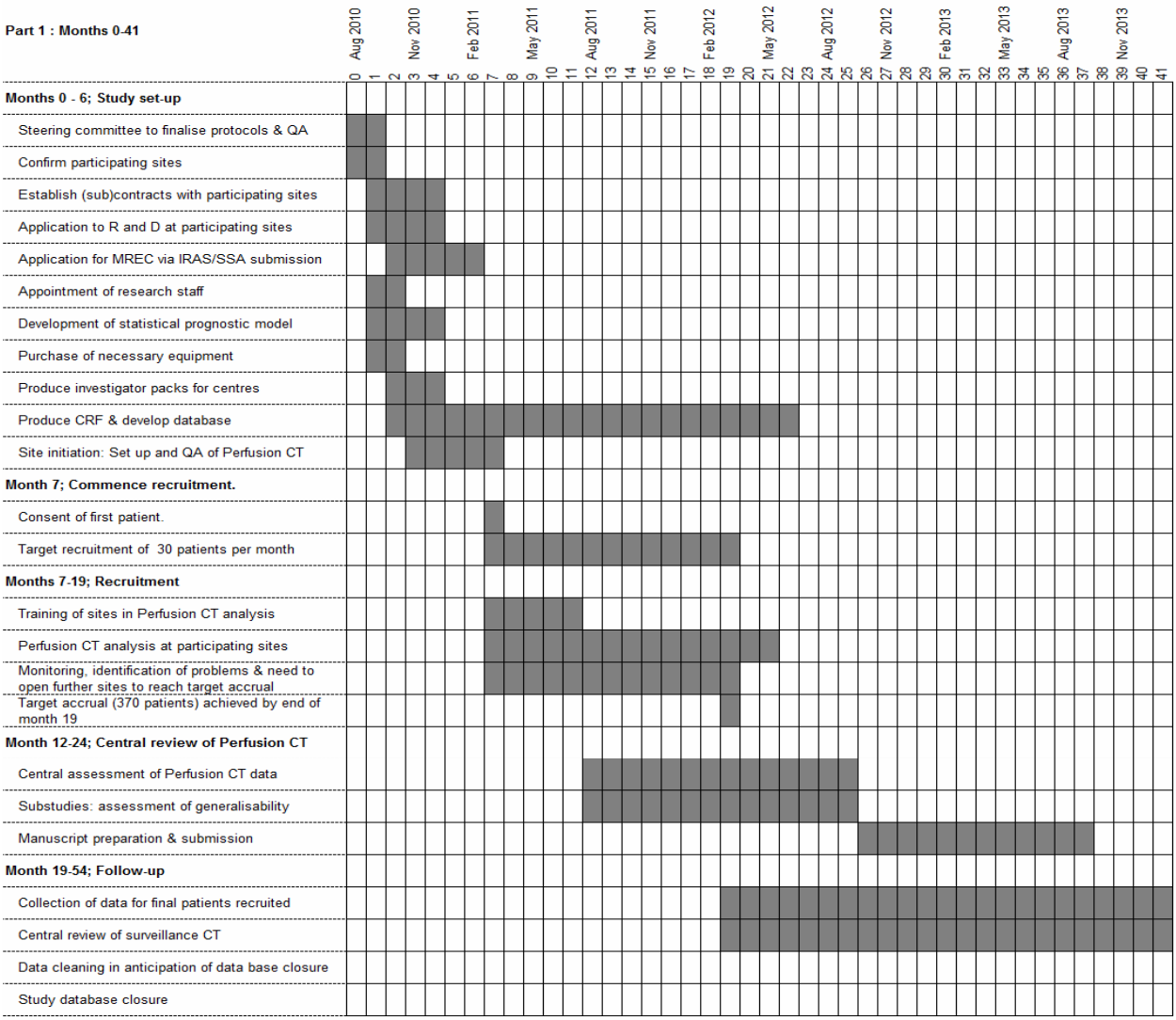
Final data analysis, assessment of the prognostic model, manuscript preparation and submission.

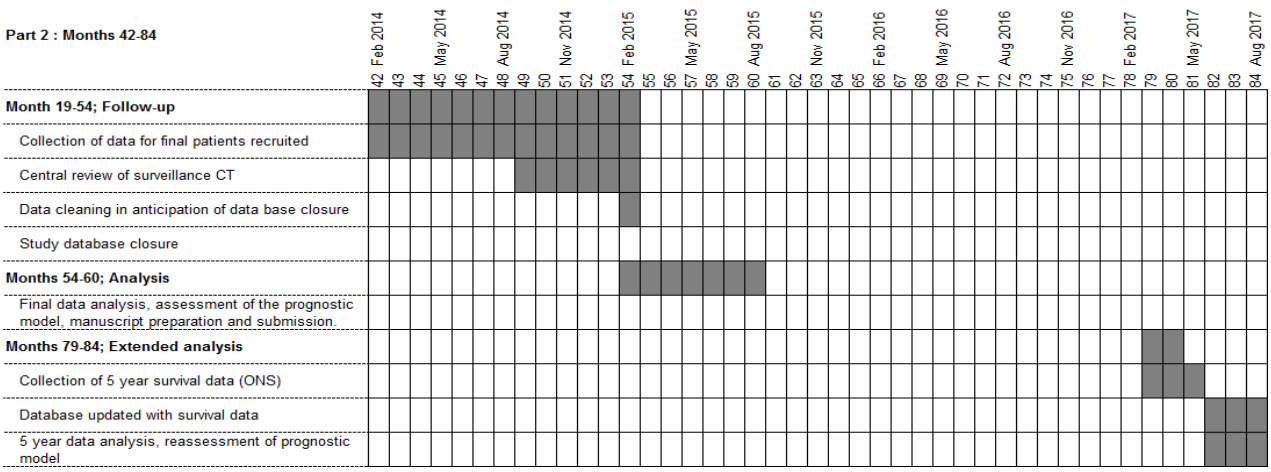
Months 79-84; Extended Analysis

Collection of 5 year survival data; database updated with survival data; 5 year data analysis, reassessment of prognostic model

Expected completion: August 2017

Appendix 7. Gantt chart showing project timetable and milestones





Appendix 8a – Investigator Statement (ISD Cancer Clinical Trials Team Copy)

PROSPeCT

The PROSPeCT study: Improving the prediction of metastatic disease in primary colorectal cancer: Prospective multicentre evaluation of a prognostic model of conventional predictive variables and novel variables derived from perfusion computed tomography

Principal Investigator Declaration

I acknowledge receipt of version 1.2 date 04 March 2011 of the PROSPeCT trial protocol (MREC approved 23 March 2011) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please return this copy to: Michelle McDermaid

ISD Cancer Clinical Trials Team,
(Partner in CaCTUS - Cancer Clinical Trials Unit Scotland),
Gyle Square,
1 South Gyle Crescent,
Edinburgh,
EH12 9EB

Fax: 0131 275 7512

Appendix 8b – Investigator Statement (Investigator Copy)

PROSPeCT

The PROSPeCT study: Improving the prediction of metastatic disease in primary colorectal cancer: Prospective multicentre evaluation of a prognostic model of conventional predictive variables and novel variables derived from perfusion computed tomography

Principal Investigator Declaration

I acknowledge receipt of version 1.2 date 04 March 2011 of the PROSPeCT trial protocol (MREC approved 23 March 2011) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please retain this copy and file in Investigator Site File.

Appendix 9 – Patient Information Sheet

To be printed on hospital headed paper

PATIENT INFORMATION SHEET

Title: PROSPeCT **Improving the prediction of metastatic disease in primary colorectal cancer: Prospective multicentre evaluation of a prognostic model of conventional predictive variables and novel variables derived from perfusion computed tomography**

ISRCTN:XXXXXXXX MREC: 10/H0713/84

Investigator: **Insert local PI here**

Introduction

You are being invited to take part in an imaging research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

1. What is the purpose of the study?
We wish to investigate if we can improve our imaging of colorectal cancer using **Computed Tomography (CT)** by performing an additional **Perfusion CT** scan to measure the blood supply to tumours. Measurement of the blood supply will provide us with information of tumour blood vessels ('angiogenesis') and tumour oxygen supply ('hypoxia'), and may potentially improve the way we assess how a tumour may behave and thus future treatment. We would like to perform the additional **Perfusion CT** scan (lasting 2 minutes) when you attend for your CT that your doctor has requested.

2. Why have I been invited to take part?
You have been invited to take part in this study because you are being investigated for a suspected or proven colorectal cancer. Approximately another 370 colorectal cancer patients like you will be asked to take part across 10 to 20 sites in the UK.

3. Do I have to take part?
No. It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form when you come for your scan or earlier if you are seen in hospital before CT. Consent will be taken in an appropriate environment. You will have the opportunity to discuss the study and ask any questions you may have. You can withdraw at any time without having to give a reason. If you decide not to take part, or if you withdraw, this will not affect the standard of care you receive. Nor will your legal rights be affected by agreeing or refusing to take part.

4. What would the study involve?
The study will involve you having a perfusion CT scan (lasting 2 minutes) in addition to the usual CT that has been requested by your doctor. This will be performed at the same time.

For a CT scan the procedure will be as follows. A needle (cannula) will be placed in an arm vein in order for an iodinated contrast 'dye' to be administered during your CT scan. You will be asked to drink water 30-60 minutes before the scan to outline the bowel. You will be given an injection of Buscopan a bowel relaxant just before the scan to improve image quality, unless you have a

contraindication to this e.g. a known allergy.Following your scan and treatment, you will be followed up by your doctor at your hospital. You will attend for clinic visits in the first three years after the perfusion CT scan, which will include a physical examination and standard blood tests.

You will have a follow-up CT scan at years 1, 2 and 3 after your treatment. . You may have a further colonoscopy at Year 3 depending on local practice at your hospital.

5. Expenses and Payments
You will not receive payment if you agree to take part in this study.

6. What are the possible disadvantages and risks of taking part?
A CT examination involves the use of X-rays and thus confers a radiation dose. The dose of the additional **perfusion** CT study is equivalent to an additional high quality whole body CT scan that patients with cancer often undergo to assess and monitor the extent of their disease.

The intravenous contrast dye may cause mild side effects including nausea and vomiting, or a rash. An allergic reaction occurs rarely and may require drug treatment. Buscopan commonly causes dry mouth; other side effects are rare including fast beating heart, shortness of breath and skin reactions.

7. What are the benefits of taking part?
There may be no immediate benefit to you. However the information we get from this study will help us to improve imaging of future patients, by providing alternative methods to changes in tumour appearance and size to assess cancer treatment. These methods will be particularly useful for assessing anti-cancer drugs that target the cancer blood supply.

8. Harm to the Unborn Child

It is possible the study procedure could cause harm to the unborn child. Pregnant women must not, therefore, take part in this study; neither should women who plan to become pregnant during the study. Women who could become pregnant should use an effective contraceptive during the study. Any woman who finds she has become pregnant within 60 days of the study procedure should immediately tell their research doctor.

9. What will happen to any samples I give?
When you were first tested for colorectal cancer, your doctor would have removed a sample of cancer tissue to make the diagnosis. You may also undergo an operation to take out the cancer. These specimens will routinely be stored in your hospital laboratory. If you agree to take part in this research study, and with your permission, we will ask the pathologist at the laboratory in your hospital to send your pathology specimens to a laboratory in London to confirm the diagnosis, and cancer extent, and carry out further tests.

10. Will any genetic testing be done?
Genetic tests will be carried out on your pathological specimen to help researchers understand more about colorectal cancer. This may help your doctors regarding ‘targeted’ chemotherapy choice in the future. Advice and counseling for this is available from your hospital doctor, and hospital services.

11. What is the alternative to taking part in the research?
You do not have to take part in this study, and can have your usual scan only.

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

13. What if something goes wrong?
We will take every care in the course of this study. If however you are harmed in this study due to someone's negligence, then you may have grounds for a legal action for which you would need to pay. There are no additional compensation arrangements for participants in this study. The normal NHS complaints mechanism is available to you if you wish to complain about any aspect of the way you are approached or treated during the course of this study. Formal complaints should be addressed to the Chief Executive (**Please insert local details here**). Should you require independent advice about making a complaint or seeking compensation, you may wish to contact the Independent Complaints Advocacy Service (ICAS) for (**Please insert local details here**).

14. Will my participation in the study be kept confidential?
Information collected about you for this study may include your name, date of birth, NHS number and/or CHI number from which it is possible to identify you as an individual however this will kept strictly confidential. This information will be securely stored at ISD Cancer Clinical Trials Units Offices in paper and electronic format under the provision of the Data Protection Act (1998).

The information from this study, including your personal medical notes, may need to be checked by authorised study personnel and possibly by national regulatory authorities.

With your permission we will inform your GP that you are taking part in this study.

We will contact the NHS Information Centre Medical Research Information Service at a later stage to obtain information that they already hold on patients treated in the UK. The data held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to provide information about your health status.

15. What will happen to the results of the research study?
Independent experts will review the progress of the research, and the results will be published in a respected medical journal as soon as there is enough information to be sure the results are reliable. The results may help to decide how to treat colorectal cancer in the future. You will not be identified in any report or publication about the study.

16. Who is organising and funding the research?
The research has been approved and funded by the National Institute for Health Research Health Technology Assessment programme.

The PROSPeCT study is being organised by the ISD Cancer Clinical Trials Team in Edinburgh. The ISD Cancer Clinical Trials Team is an NHS National Services Scotland organisation that receives funding from the Scottish government. All treatment is provided by the NHS.

Your doctor will not receive any personal financial rewards for including you in this study.

17. Data Retention

Data generated by this study will be retained by the ISD Cancer Clinical Trials Team for at least 15 years after the end of the trial. It will be disposed of securely.

18. Who has reviewed the study?

This study has been reviewed by the Central London Research Ethics Committee 2. This is an independent group of people with responsibility for advising on whether NHS research complies with recognised ethical standards.

19. Contact for further information

Your study doctor or research nurse will be happy to answer any questions you have about this study. You can telephone them on the numbers shown below, or speak to them again when you come to the clinic.

Your Study Doctor is:	
Contact Number:	
Your Research Nurse is:	
Contact Number:	

Thank you for taking the time to read this information sheet and for considering participating in this research study.

Appendix 10 – Informed Consent Form

Study Number: Patient Identification Number for this study: | | | | | |

CONSENT FORM

Title of Project: ***Risk stratification by Perfusion CT at primary colorectal cancer staging: Multicentre evaluation of a prognostic model*** **MREC no: 10/H0713/84**

Name of Researcher: Insert local PI

I (name)……

Please **initial boxes**

1. I confirm that I have read and understand the patient information sheet dated **12th January 2011 version 1.1** for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities and by members of the ISD Cancer Clinical Trials Team working on behalf of King's College London, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I understand that data, as described in the Patient Information Sheet, will be passed to authorized individuals working on behalf of the King's College London. I understand my name will be given when I join the study and thereafter I will be identified by a unique trial number, initials and date of birth. Any information passed to the regulatory authorities, ethics committees and drug manufacturers will not identify me by name. ☐
5. I understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to provide information about my health status. ☐
6. I understand that research laboratory staff may look at my pathology specimens where relevant to my taking part in research. I give permission for the researchers to have access to my specimens. ☐
7. I agree to my GP being informed of my participation in this study. ☐
8. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 copy for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 11 List of Expected Adverse Reactions

CT Contrast Agent

A list of adverse reactions expected following CT contrast agent injection is given in the table below.

Very common: >1 in 10 users
Mild discomfort during injection Hot flush Temporary bad taste in mouth
Common: 1 in 10-1000 users
Nausea Vomiting Hives
Common: 1 in 10-10 000 users
Dizziness Trembling Low blood pressure Difficulty breathing Dry mouth Tingling skin, redness, itching, rash Racing pulse Cough, throat tightening, chills, headache Hay-fever Painful urination
Very rare: 1 in 10 000 users
Anxiety, sleepiness, loss of memory Confusion Speech disorders Muscle cramps, numbness, paralysis Absent mindedness Red eye, sight problems Irregular heart beat Hypersensitivity reaction: swelling of throat, bronchospasm Anaphylactic shock: respiratory arrest, cardiac arrest Acute renal failure Diarrhoea, incontinence

Contraindications to CT contrast agent administration include:

Proven hypersensitivity to iodine-containing contrast media

Manifest hyperthyroidism

Buscopan

A list of expected side effects following administration of Buscopan injection is given below:

Injection site pain

Dry mouth

Constipation

Low blood pressure

Dizziness

Flushing

Accommodation disorders

Tachycardia

Urinary retention

Dyshidrosis

Hypersensitivity reaction

Anaphylactic shock

Contraindications to Buscopan administration:

Myasthenia gravis

Megacolon

Narrow angle glaucoma

Tachycardia

Mechanical stenoses of the GI tract or paralytic ileus

Appendix 12 – The Principles of ICH Good Clinical Practice

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.