TRIAL PROTOCOL

CReST2

ColoRectal Stenting Trial 2 - Uncovered vs covered endoluminal stenting in the acute management of obstructing colorectal cancer in the palliative setting.

V1.0 19th December 2016

ABSTRACT

Colorectal cancer is the second most common cause of cancer death in the UK. Each year around 15% of people with colorectal cancer present with an obstruction. Surgery to resect the blockage is the usual treatment for the relief a bowel obstruction. However, in many patients with colorectal cancer their age, general health and the advanced state of their cancer means that they are not able to withstand this type of surgery. Such patients may benefit from the minimally invasive technique called stenting. Patients are living longer with stents *in situ,* so choosing the right design of stent is important to maximise quality of life. The type of stent may also affect the rate of reintervention, and therefore costs. Two designs of stent are in common use in the UK today. The majority of stents used to relieve an obstruction in people with colorectal cancer are uncovered, i.e. the stents are made of bare metal. The remaining stents have a plastic covering designed to reduce the risk of the tumour growing into the lumen and causing blockage to the bowel. There is currently little evidence on which type of stent is most effective in patients with obstruction. Therefore, the CReST2 trial will investigate which stent design, covered or uncovered, is most efficacious in improving the quality of life in palliative patients with bowel obstruction arising from colorectal cancer.

CReST2 is a five year NIHR funded phase III multicentre randomised controlled trial. 350 patients will be randomised to receive either a covered or uncovered stent. To reduce bias, patients and all medical personnel except the person placing the stent will be blinded to allocation.

The co-primary outcomes measures are Quality of Life for palliative colorectal patients requiring a stent, evaluated by the QLQ-C30 questionnaire at 3 months post-stenting and stent patency measured at 6 months post-stenting. Patients will be followed up for a period of two years.

Sponsor reference number	G00314
ISRCTN number	TBC
REC reference number	17/NW/0051

CReST2 is funded by the National Institute for Health Research's HTA Programme

Protocol development and sign off

Protocol Contributors
The Trial Management Group of the CReST2 trial wrote the protocol.

CI Signature Page	
This protocol has been approved by:	
Trial Name:	CReST2
Protocol Version Number:	V1.0
Protocol Version Date:	19 December 2016
CI Name:	Professor James Hill
Trial Role:	Chief Investigator
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement:
Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

TRIAL COMMITTEES AND CONTACT DETAILS

TRIAL MANAGAMENT GROUP	
Surgery	
Professor James Hill	Consultant General and Colorectal Surgeon
Central Manchester University Hospitals NHS Trust , Manchester	0161 276 4286 James.Hill@cmft.nhs.uk
Professor Dion Morton	Professor of Surgery
University Hospitals Birmingham NHS Foundation Trust, Birmingham	0121 627 2276 Dion.Morton@uhb.nhs.uk
Miss Anne Pullyblank	Consultant General and Colorectal Surgeon
North Bristol NHS Trust, Bristol	07799 584 392 anne.pullyblank@nbt.nhs.uk
Ms Nicola Fearnhead	Consultant Colorectal Surgeon
Addenbrookes Hospital	01223 348219 Nicola.fearnhead@addenbrookes.nhs.uk
Radiology	
Professor Clive Kay	Consultant GI Radiologist
Bradford Teaching Hospitals NHS Foundation Trust, Bradford	01274 382 407 clive.kay@bradfordhospitals.nhs.uk
Dr Andrew Lowe	Consultant GI Radiologist
Taunton and Somerset NHS Foundation Trust, Taunton	01823 342 319 andrew.lowe@tst.nhs.uk
Dr Hans-Ulrich Laasch	Consultant Radiologist
The Christie NHS Foundation Trust, Manchester	0161 446 3896 hans-ulrich.laasch@christie.nhs.uk
Statistics	
Professor Richard Gray	Professor of Medical Statistics
Clinical Trial Service Unit, University of Oxford	01865 743 537 richard.gray@ctsu.ox.ac.uk
Dr Kelly Handley	Medical Statistician
Birmingham Clinical Trials Unit, University of Birmingham	01214159114 K.Handley@bham.ac.uk
Trial Management	
Professor Jonathan Deeks	Professor of Biostatistics
Birmingham Clinical Trials Unit, University of Birmingham	0121 414 5328 J.Deeks@bham.ac.uk
Dr Laura Magill	Clinical Trials Team Leader
Birmingham Clinical Trials Unit, University of Birmingham	0121 415 9105 e.l.magill@bham.ac.uk

TRIAL MANAGAMENT GROUP CONTINUED	
Health Economist	
Dr Andrew Sutton	Associate Professor in Decision Analytic Modelling
Leeds Institute of Health Sciences, University of Leeds	0113 343 9814 A.J.Sutton@leeds.ac.uk
Patient Representative	
Mr J Tobutt	Patient Representative

Data Monitoring Committee	Trial Steering Committee
Professor Gordon Carlson Consultant General and Colorectal Surgeon Salford Royal NHS Foundation Trust	**Professor Derek Alderson** Professor of Colorectal Surgery Retired
Dr Louise Hiller Principal Research Fellow WMS – Clinical Trials Unit, University of Warwick	**Dr Ly-Mee Yu** Lead Trial Statistician Primary Care Clinical Trials Unit University of Oxford
Professor Stuart Taylor Professor of Medical Imaging University College Hospital, London	**Professor Steve Halligan** Professor of Gastrointestinal Radiology University College Hospital, London
	Dr Philip Bell Patient Representative

Administrative Information

Sponsor	
Central Manchester University Hospitals NHS Foundation Trust	0161 276 4791 (Trust HQ) 0161 276 3565 (Research and Innovation)
Cobbett House, Oxford Road, Manchester, M13 9WL	Research.getinvolved@cmft.nhs.uk

Chief investigator	
Professor James Hill	Consultant General and Colorectal Surgeon
Central Manchester University Hospitals NHS Trust , Manchester	0161 276 4286 James.Hill@cmft.nhs.uk

Sponsor's Medical Expert for the Trial	
Professor James Hill	Consultant General and Colorectal Surgeon

Trial Office Contact Details	
Dr Laura Magill	Clinical Trials Team Leader
Birmingham Clinical Trials Unit, University of Birmingham	0121 415 9105 e.l.magill@bham.ac.uk
CReST2 Trial Office	0121 415 9103 Crest2@trials.bham.ac.uk

TRIAL SUMMARY

CReST2 - ColoRectal Endoscopic Stenting Trial 2 - Uncovered vs covered endoluminal stenting in the acute management of obstructing colorectal cancer in the palliative setting

Trial Design

CReST2 is a blinded, multi-centre randomised controlled trial with a 12 month internal feasibility to assess recruitment viability.

Objectives

To compare the effect of uncovered and covered stents on the quality of life of people with inoperable obstructing colorectal cancer who are managed by undertaking an urgent decompression and stenting. The efficacy of each type of *in-situ* stent will be measured alongside the technical success, rates of endoscopic re-intervention, the need for a stoma, overall survival and cost effectiveness.

Participant Population and Sample Size

A minimum of 350 patients with colorectal cancer who are managed with a palliative intent and who require an urgent decompression of their colorectal obstruction. These participants will be recruited from a minimum 20 NHS sites across the UK and overseas.

Outcome Measures

Primary:

The Quality of Life at 3 months measured using the QLQ-C30 global health score

Stent patency up to 6 months post-stenting.

Secondary:

The stenting success rate in each arm as defined by initial clinical relief of bowel obstruction

Time to onset of short, intermediate and long-term stent related complications, measured at 30 days (short term), 1-3 months (intermediate term) and 3-12 months (long term) post-stent

Stent related complication rates of patients undergoing chemotherapy

The cumulative frequency and duration of stoma formation in each arm

Overall survival

Cost effectiveness using the outcome measure of cost per quality adjusted life year.

Key Eligibility Criteria

Patients over 16 years of age, who are not pregnant and who present with colonic obstruction and radiological features consistent with a carcinoma which requires decompression. These patients will have colorectal cancer and the stenting procedure will be considered to be a palliative measure for the relief of the obstruction. Patients will suffer from one, or a combination of more than one of, the following categories:

- unresectable local disease
- unresectable metastatic disease
- considered unfit for surgery

Intervention

Patients will be randomised to undergo the relief of their colonic obstruction by the insertion of either an uncovered or covered stent.

Trial Schema

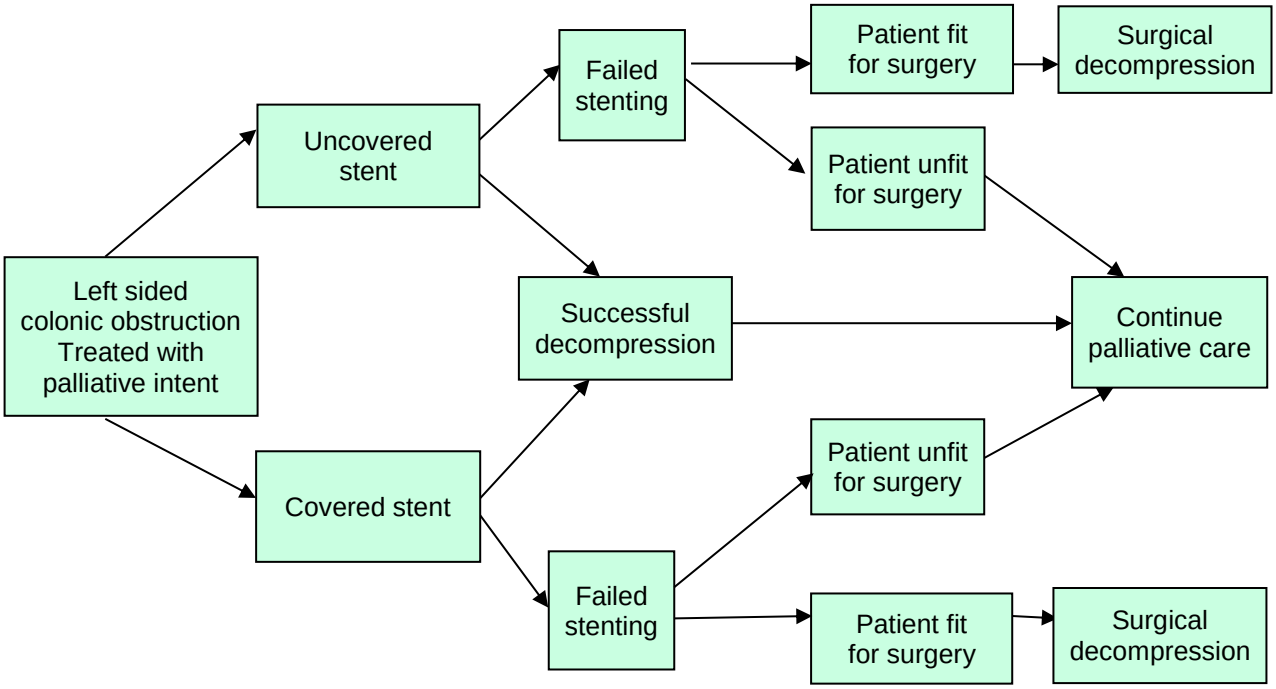

TABLE OF CONTENTS

1. Background and Rationale

1.1. Background

With approximately 40,000 new cases registered each year, colorectal cancer is one of the most common cancers in the UK. Almost three quarters of colorectal cancer occurs in people aged 65 or over. Colorectal cancer is the second most common cause of cancer death in the UK.

Each year around 15% of people with colorectal cancer present with an obstruction which has resulted from the tumour growing and blocking the lumen of the bowel (1). Unless this blockage is relieved, the continual impaction of faecal matter leads to painful distention and if left untreated the person's bowel will eventually perforate, leading to the development of peritonitis, sepsis and death. Surgery to resect the blockage is the usual treatment for the relief a bowel obstruction. However, in many patients with colorectal cancer their age, general health and the advanced state of their cancer means that they are not able to withstand this type of surgery.

The CRest1 trial has shown that such patients may benefit from the minimally invasive technique called stenting. In this technique a collapsed flexible metal tube is inserted into the bowel under radiological guidance. Once in place this tube is expanded and pushes back the obstruction thus relieving the blockage. Previous work by our group has shown that stenting is an effective and viable treatment to relieve obstructions in people with colorectal cancer. Not only does stenting remove the requirement for a general anaesthetic, but it provides an immediate relief of symptoms whilst avoiding the need for a stoma.

After insertion in this patient group the stents are left *in situ.* Unfortunately, stent related complications have been reported in over one third of patients and can include perforation of the bowel, the stent becoming obstructed or migrating from where it is placed (2-6). Some people have suggested that the nature of the stent can increase complication rates in some people undergoing chemotherapy.

As people with colorectal cancer are living longer with a stent *in situ*, choosing the best stent is becoming increasingly important to maximise the quality of life experienced by people with obstructing colorectal cancer. As some types of stent have been suggested to be more likely to require re-intervention, selecting the most efficacious stent may well generate significant cost savings for the NHS.

1.2. Trial Rationale

1.2.1.Current evidence

Two designs of stent are in common use in the UK today. Currently nine out of ten stents placed to relieve an obstruction in those with colorectal cancer are uncovered, i.e. the stents are made of bare metal. The remaining stents in use in the UK are covered stents. These stents have a plastic covering designed to reduce the risk of the tumour growing into the lumen and causing blockage to the bowel. A systematic review/meta-analysis identified only one randomised trial comparing covered with uncovered stents. The systematic review (2) reported that uncovered stents were associated with a lower late migration rate than covered stents, (relative risk 0.25; 95% CI 0.08, 0.80; P = 0.02), a higher tumour in-growth rate (relative risk 6.0; 95% CI 2.2, 16.1; P = 0.0004) and a prolonged stent patency (weighted mean difference 15.3 days; 95% CI 4.3, 26.4; P = 0.006). There was no significant difference in technical success, clinical success, tumour overgrowth, early migration, perforation or overall complications between the two groups. Only one of the studies reviewed was randomised (5). In this trial of 151 patients with malignant colorectal obstruction (Park 2010), complications from cancer infiltration were more frequent in the uncovered stent group (14.5% vs 3.8%) though late stent migration was higher in the covered stent group (21.1% v 1.8%). Mean patency did not differ between the two groups (P=0.5). No Quality of Life data were collected.

Given the little available evidence, no conclusions can be drawn on the comparative benefits of covered versus uncovered stents and, worldwide, there is no guidance on which stents are better in

treating this condition. **CReST2** is designed to determine which stent design, the uncovered or covered stent, is the most efficacious in improving the quality of life in patients with bowel obstruction arising from colorectal cancer.

1.2.2. Trial design

In order to minimise bias, **CReST2** has been designed as a double blinded randomised trial. This means that whilst the person inserting the stent will know which type it is, they will be instructed not to reveal this information to the patient, not to record the type of stent inserted in the patient's notes and not to inform the clinical team looking after the patient. In this way, patients and clinicians undertaking the follow up will not know which type of stent has been used in that patient.

The nature of the stent used to relieve the bowel obstruction in each patient will be recorded in the trial office. The trial office will reveal the nature of the stent inserted should there be a valid clinical or safety need.

In order to ensure that **CReST2** will be able to recruit sufficient participants to ensure that the conclusions reached at the end of the trial are robust and reliable, recruitment during the first 12 months will be closely monitored. The criteria to determine if **CReST2** continues past this 12 month feasibility stage or is halted due to futility are set out elsewhere in this protocol.

1.2.3.Treatment

People with obstructing colorectal cancer undergoing palliative care will be randomised to undergo decompression with either a covered or uncovered stent. The stent will be placed as a joint endoscopic/fluoroscopic procedure by individuals experienced in performing colonic stenting**.**

2. Aims, Objectives and Outcome Measures

2.1. Aims and Objectives

The aim of the **CReST2** trial is to determine if the use of covered stents for palliative patients with obstructing colonic cancer, ie where the intention is to leave the stent in situ, will result in an improved Quality of Life when compared to the use of uncovered stents.

The aim of the internal feasibility trial is to assess if recruitment to the randomised interventions is feasible and to assess clinician equipoise.

2.2. Internal Feasibility

2.2.1.INTERNAL FEASIBILITY STUDY AIM

The first 12 months of recruitment will form the internal feasibility study. The aim of the internal feasibility is to assess the rate of recruitment at 12 months post recruitment start and to assess clinician equipoise in order to determine if it is feasible for the study to continue or not.

2.2.2.INTERNAL FEASIBILITY STUDY OBJECTIVES

To determine recruitment rates and to assess if clinical equipoise exists in the use of stent type.

2.2.3.INTERNAL FEASIBILITY STUDY STOP-GO CRITERIA

The feasibility of the trial will be assessed at 12 months post start of recruitment. The STOP-GO criteria are:

1. Completeness of trial-specific data of at least 80%

   The successful completion and return rates of the case report forms will be measured during the feasibility trial. At the end of the feasibility phase the return rate of scheduled CRFs should be over 80%.

2. Validation of the HES data against the trial-specific data collection

   Routinely collected HES data will be validated against the trial-specific collected data. The HES data should be of a standard at least equal to that of the trial data, to warrant its continued use.

3. At least 75% of the 12 month target recruitment of patients randomised.

   If at least 75% of the 12 month patient recruitment target of patients is randomised, (12 month target is 70, therefore 52 patients would be required to be randomised), or a recruitment rate of ≥6 patients randomised per month is achieved, we would consider it feasible to continue with recruitment and achieve the sample size within the 3 year period.

4. At 12 months post-recruitment start, 15 centres open to recruitment.

At the end of the feasibility phase, the Trial Management Group will prepare a report detailing recruitment information and data gained from screening logs. The independent Trial steering Committee (TSC) will be asked to make recommendations on whether they think that recruitment to the feasibility study has shown that recruitment to a full phase III study is feasible. Data from the feasibility phase will not be unblinded or reported to the Trial Management Group or TSC but carried forward – if the study continues – to the full trial. If recruitment is found to be feasible and acceptable, then the study will move seamlessly into a full phase III study.

2.3. Full Phase Trial Primary Objectives

The primary objectives of the **CReST2** trial are to determine:

1. Is the Quality of Life for palliative colorectal cancer patients requiring a stent dependent on whether the stent is covered or uncovered?
2. Is the efficacy of the stenting procedure dependent on whether the stent is covered or uncovered?

2.4. Full Phase Trial Secondary Objectives

The secondary objectives are to determine:

1. If the technical success rates are different between covered and uncovered stents.
2. If the incidence of stent-related complications (perforation, blockage, migration) are different between covered and uncovered stents.
3. The rate of endoscopic re-interventions in each arm.
4. Whether the stent type used affects the stoma rate
5. If the stent type used impacts on overall survival.
6. The cost effectiveness of implementing covered stents compared to uncovered stents

2.5. Primary outcome measures:

The primary outcome measures are:

1. Quality of Life at 3 months post-stenting (or at 30 days for patients dying before 3 months) as evaluated by the QLQ-C30 questionnaire and compared with the baseline.
2. Stent patency post-stenting (time to failure by logrank analysis).

2.6. Secondary outcome measures

The secondary outcome measures are:

1. The stenting success rate in each arm as defined by clinical relief of bowel obstruction.
2. Time to onset of short, intermediate and long-term stent related complications, measured at 30 days (short term), 1-3 months (intermediate term) and 3-12 months (long term) post-stent.
3. Stent related complication rates of patients on chemotherapy in each arm.
4. The cumulative frequency and duration of stoma formation in each arm.
5. Overall survival
6. Cost effectiveness using the outcome measure of cost per quality adjusted life year.

3. Trial Design and Setting

3.1. Trial Design

CReST2 is double-blind, multi-centre, randomised controlled trial with a built in 12 month feasibility phase.

Patients, and the clinician responsible for assessing outcomes, will be blinded to the randomised allocation.

A minimum of 350 patients will be randomised in a 1:1 ratio to undergo stenting with either a covered or uncovered stent.

3.2. Trial Setting

CReST2 will operate in NHS centres or equivalent overseas sites; participating centres must have placed at least 30 stents for the treatment of obstructing colorectal cancer, with participating individual radiologists or endoscopists, having placed at least 10.

Centres which have performed less than 30 stents may be eligible to participate in **CReST2** after review of their stenting data by the **CReST2** clinical leads.

Members of the CReST TMG have established a network of 39 units who have randomised patients into the preceding trial, CReST1. These units have individuals who are skilled and experienced in performing colonic stenting in the acute setting and who have demonstrated good compliance with the **CReST1** study protocol. Clinicians at these sites have demonstrated their ability to successfully randomise patients and have high completion rates (>90%) of case report forms. These Principal Investigators have been contacted about the **CReST2** study and 24 sites have already indicated their support.

3.3. Inclusion Criteria

- Patients presenting with obstructing colorectal cancer which is to be treated with palliative intent, where this includes patients with one or more of the following:
  - unresectable local disease
  - unresectable metastatic disease
  - considered unfit for surgery
  - or a combination of the above.
- Aged 16 years or older
- Patient able and willing to give written, informed consent or have consent provided by a legal representative

3.4. Exclusion Criteria

- Patients with impending or established perforation of the colon
- Patients with low rectal cancer, i.e. a carcinoma in the lower third of the rectum
- Patients being treated or considered for treatment with antiangiogenic drugs (e.g. bevacizumab)
- Pregnant patients.

4. Consent

It will be the responsibility of the Investigator to obtain written informed consent for each participant prior to performing any trial related procedure. A REC approved Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the potential participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The

participant will be given the opportunity to ask questions and have them answered to their satisfaction.

If the participant expresses a wish to participate in the trial they will be asked to read then sign and date the latest version of the Informed Consent Form (ICF). The Investigator, or delegate, will then sign and date the form. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's unique trial identification number will be generated and this number recorded on the Informed Consent Form maintained in the ISF. If the participant has given explicit consent (detailed on the ICF), then a copy of the signed ICF will be sent to the **CReST2** Trial Office.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received.

Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain. With the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

Electronic copies of the PIS and ICF will be available from the **CReST2** Trial Office and for UK sites will be printed or photocopied onto the headed paper of the local institution. Details of all participants approached about the trial will be recorded by the local trials team on the Participant Screening Log.

5. Enrolment and Randomisation

5.1. Enrolment

Following **CReST1** a large UK-wide network of units has been established which now have systems in place for the identification, selection and randomisation of patients with large bowel obstruction who require stent insertion. We also hope to establish international collaborations.

Potential participants in **CReST2** will be identified from both routine and emergency settings. In routine settings, patients receiving palliative care may have progression of their cancer to the point of obstruction. If an obstruction develops, stenting will be undertaken to relieve the obstruction. Potential participants for **CReST2** may also present as an emergency admission, either with a new diagnosis of colorectal cancer, or patients who have been previously diagnosed with incurable colorectal cancer and who have then developed an obstruction.

The diagnosis and stratification as probably palliative or potentially curative is a standard part of the assessment of both groups of patients. If patients are considered probably palliative cases, and found to have an obstruction which it is believed would be resolved by stenting, the person will be eligible to participate in **CReST2**.

Patients who fulfil the inclusion criteria and who have their eligibility confirmed by medically qualified personnel will be asked to consent to enter the study. Eligible patients will be provided with a REC approved information sheet by their responsible clinician who will provide a comprehensive verbal explanation of the study and the possible treatment options available to that patient. Throughout the consent process, potential participants will be encouraged to ask questions and will be reminded that they can withdraw at any time without their clinical care being affected.

Written consent will be obtained from the participant and this will be confirmed by the trials office prior to randomisation.

5.2. Randomisation method and stratification variables

Randomisation can only occur once all eligibility criteria are collected, consent confirmed and stratification variables determined. To minimise any potential bias, following consent all participants will complete the baseline Quality of Life questionnaire which will be returned to the clinical staff prior to randomisation.

Participants will be randomised at the level of the individual in a 1:1 ratio to either covered stent or uncovered stent. A minimisation algorithm will be used to ensure balance in the treatment allocation over the following variables:

1. Age
2. WHO performance status
3. Tumour site
4. Indication for palliation (unresectable local disease; unresectable metastatic disease; unresectable local and metastatic disease; considered unfit for surgery; unfit for surgical decompression or a combination of these) .

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Investigators will keep their own study file log which links patients with their allocated trial number in the **CReST2** Patient Recruitment and Identification Log. The Investigator must maintain this document, which is not for submission to the Trials Office. The Investigator will also keep and maintain the **CReST2** Screening Log which will be kept in the ISF, and should be available to be sent to the Trials Office upon request. The **CReST2** Patient Recruitment and Identification Log and **CReST2** Participant Screening/Enrolment Log should be held in strict confidence.

If the participant has agreed, the participant's GP should be notified that they are in the **CReST2** trial, using the **CReST2** GP Letter.

5.3. Telephone and online randomisation

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at https://www.trials.bham.ac.uk/CReST2). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study as detailed on the **CReST2** Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service ((0044) 0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

After informed consent has been received and eligibility confirmed, the participant can be randomised into the trial. Randomisation notepads are provided in the **CReST2** Site File and should be used to collate the necessary information prior to randomisation. After all the necessary details have been provided, the treatment allocation will be specified at the end of the telephone call, or in the final screen of the website program.

Patients are entered into **CReST2** by contacting the randomisation service either by:

Telephone (Freephone 0800 9530274)
or
Online (https://www.trials.bham.ac.uk/CReST2)

Following randomisation, the patient's GP should be notified that they are in the **CReST2** trial and a specimen "Letter to GP" is provided for this purpose.

5.4. Blinding of treatment allocation

Only the trial office and the radiologist or endoscopist responsible for stent insertion will be made aware of the randomised allocation; the patient, the clinician responsible for follow-up and all other site personnel will remain blinded to the type of stent placed. The clinician inserting the stent should obtain the randomisation allocation before they place the stent. The nature of the stent placed should not be recorded in the patient's notes. Should medical necessity dictate then this information can be obtained from the trials office.

Immediately following randomisation, the radiologist/endoscopist will be informed of the treatment allocation via an automatic email from the **CReST2** Trial Office. A confirmatory e-mail will also be sent to the local Principal Investigator, the research nurse and the clinician responsible for the care of the patient. These emails will state only that the patient has been entered into the CReST2 trial; the randomised allocation will not be released.

The radiologist/endoscopist will be asked only to record in the patient's notes that they placed the stent as part of the CReST2 trial, and not the nature of the stent (i.e. covered or uncovered). This is in line with all legal and governance requirements. The **CReST2** Trial Office will supply participating sites with labels to be used in the patient's notes to confirm that the patient is in a clinical trial and who to contact in the event of a medical emergency which necessitates unblinding.
It should also be recorded in the patient's notes that, should clinical necessity or patient safety demand, then this information will be released from the **CReST2** trial office on a per patient basis.

5.5. Unblinding procedure

Unblinding is permissible if required due to an urgent clinical need or patient safety issue.

The Principal Investigator (PI), or co-investigator(s) listed on the delegation log in the PI's absence, will have a secure login and password to access the **CReST2** online system where the allocation will be revealed following entry of the necessary details. An email will be generated to alert the CReST2 Trial Office that the investigator has been unblinded.

If it becomes necessary to unblind, where possible, members of the site research team will remain blinded, subject to clinical need. Unblinded participants will remain in the trial, and continue with trial follow-up assessments.

6. Trial intervention

6.1. Treatment

The stents being used in **CReST2** are all existing, commercially available, marketed products which are licensed and CE marked. Participating trusts can select the stent of their choice from a range of suitable stents approved for use within the trial by the **CReST2** Trial Management Group. This will allow practitioners inserting stents to use the stent type that they are most familiar with.

6.2. Stent Supply and Storage

6.2.1.Treatment Supplies

Participating Trusts will obtain the approved stents using their usual purchasing procedures

6.2.2.Packaging and Labelling

The stents will be kept in their original manufacturers packaging.

6.2.3.Stent Storage

The covered and uncovered stents will be kept in controlled conditions at the participating trusts, as per local practice and made available for use dependent upon allocation.

Accountability Procedures

Compliance with treatment allocation will be monitored by the CReST2 Trial Office by comparing the nature of the stent recorded as being inserted on a dedicated trial data collection form with that stated in the randomisation allocation.

6.3. Treatment Modification

Clinicians will use their usual criteria to determine if an intervention is deemed to have failed clinically and if a re-intervention is necessary. This information will be recorded in the patient's notes and on the appropriate CRF (depending on the timing of stent failure this will be either the Stent Insertion CRF, the Stent Follow-Up CRF or the SAE CRF). The nature of any re-intervention will be at the discretion of the treating clinician who will use their skill, knowledge and experience to determine the most appropriate treatment.

7. Trial procedures and assessments

7.1. Summary of assessments

Figure 2: CReST2 Assessments Schedule

Outcome Measure	**Timepoint (post-stent)**						
	Baseline	30 days	3 months	6 months	12 months	18 months	24 months
QoL: QLQ-C30, QLQ-C29, EQ-5DL	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Stent complications		**x**	**x**	**x**	**x**		
Stoma formation		**x**	**x**	**x**	**x**		
Endoscopic re-intervention			**x**	**x**	**x**	**x**	**x**
Resource Usage							
Adverse events	**Monitor throughout study**						
Survival					**x**		

7.2. Schedule of Assessments

Potential participants will be identified from both the routine and emergency setting, i.e. people with colorectal cancer presenting to A&E departments with a large bowel obstruction, and those with pre-existing colorectal cancer in whom the stenting procedure to relieve an obstruction is planned.

Patients in whom a large bowel obstruction is suspected will undergo a standard CT scan of their abdomen and pelvis. This will allow staging of the primary and secondary disease. Patients with a symptomatic stricture secondary to colorectal cancer who are identified as having incurable disease and patients assessed as being unfit for major surgery but in whom stenting is seen as a viable treatment are eligible to participate in **CReST2**.

Those patients deemed eligible will be approached for entry into the trial by a member of the **CReST2** research team at site, usually either the surgeon, radiologist or endoscopist, and the nature of the trial introduced to them. Those patients who express an interest in participating will be given a REC approved Patient Information Sheet (PIS) which they will be encouraged to read. Following a discussion during which the potential participant will be encouraged to ask questions the participant will be given a suitable period of time to consider participation in the **CReST2** trial.

Those who consent to participate in **CReST2** will sign a consent form, complete the baseline quality of life questionnaires, and have their baseline data collected. The patient's notes will be annotated to state that this patient is participating in the **CReST2** trial.

7.3. Trial Procedures

Approved types of both 'covered' and 'uncovered' stents will be available in the radiology suite. Once the interventional radiologist, endoscopist or designated member of the research team has obtained the **CReST2** allocation, the correct type of stent (ie uncovered or covered) will be drawn from the theatre supply. This stent will be inserted as a joint endoscopic/fluoroscopic procedure by individuals experienced in performing colonic stenting. The person placing the stent will be asked to record that a

stent has been placed in the patient's notes, but not if the stent was covered or uncovered. This will help ensure that both the responsible clinician and patient will be blinded to the type of stent inserted.

Following stent insertion the centre's standard care pathways will be followed. As the trial participants are likely to be a disparate group of patients it is not possible to be prescriptive about the standard care pathway and they will be managed symptomatically. Nonetheless, patients will be regularly reviewed in the outpatient clinic. Should this appointment coincide with a follow-up time point the participant will be asked to complete a quality of life questionnaire and return it to the staff before they leave. Quality of life questionnaires will be completed at 1,3,6,12,18 & 24 months post stent insertion. If the follow-up time point does not coincide with an Outpatient's appointment then the follow-up questionnaire will be sent to the participant's home address accompanied by a pre-paid envelope addressed to the trial's office.

Once patients have been randomised, their local patient identifiers and personal information such as age, gender and date of recruitment will be transferred to the informatics department of University Hospitals Birmingham (UHB). The informatics team will link this information to HES and run the necessary quality assurance checks to confirm linkage. Once the linkage has been confirmed the informatics department will run a monthly check on the new HES records (once transferred), to identify whether patients have used any hospital services including the number of hospital outpatient visits, A&E attendances and inpatient admissions. These updates will include details of the hospital activity including reasons for visits, hospital length of stay, type of admission, and interventions performed. UHB will identify key information on outcomes and return pseudo-anonymised data to the clinical trials unit. The results data will be held on a secure SSL server within the University of Birmingham. Trial office staff will have access to the data *via* a secure university network. Access to these data will be limited to members of the trial team. Data will be owned by the Trial Management Group.

Linkage to ONS records will also be provided detailing date and the causes of death as listed on the death certificate.

8. Adverse Event Reporting

8.1. Reporting Requirements

Selected AEs will be recorded and reported for the **CReST2** trial. AEs will be identified through enquiries made at study time points and through any emergency admissions. Stent related complications include perforation, obstruction and migration. Each of these will be classified as Serious Adverse Events and the trials office should be notified about these events by the site completing and returning the **CReST2** SAE form as soon as they become aware of them. Data collected *via* SAE reports will include information about the outcome of the complication and whether it could be treated endoscopically.

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant and this should be documented in the source data with reference to the protocol.

8.2. Adverse Events

AEs are commonly encountered in people with obstructing colorectal cancer who are managed palliatively through decompression by stenting.

As these events are well characterised, it is highly unlikely that this trial will reveal any new safety information relating to the stenting procedure. The recording of selected AEs will therefore not affect the safety of participants or the aims of the trial.

8.3. Serious Adverse Events

Events which meet the definition of serious will be collected and recorded in the participant notes and the SAE CRF. In addition, SAEs will be reported to the trials office immediately and within 24 hours of the site being made aware of the event.

Within the **CReST2** trial, there are certain events which are expected SAEs and which should be notified to the CReST2 Trial office as soon as the site becomes aware of the event. These expected SAEs include, but are not limited to:

- Failure to deploy the stent
- Bowel perforation
- Stent migration
- Re-obstruction

8.4. Monitoring pregnancies for potential Serious Adverse Events

Women who are pregnant at the time of randomisation will not be eligible to participate in **CReST2**.

In the event that a participant becomes pregnant during the SAE reporting period a pregnancy notification form will be completed and returned to the CReST2 Trial Office. Details of the outcome of the pregnancy will be provided on a follow-up pregnancy notification form.

8.5. Reporting period

The reporting period will commence when the participant gives consent to participate in **CReST2**.

The reporting period will cease 24 months after insertion of the colorectal stent.

Details of all AEs (except those listed above) will be documented and reported from the date the participant gives consent to participate in **CReST2**. The requirement for documentation and reporting will cease 30 days after the due date of the two year post-stenting quality of life questionnaire.

8.6. Reporting Procedure – At Site

8.6.1. Adverse Events

AEs are commonly encountered in people with colorectal cancer who are managed with a palliative intent and who require decompression of their colorectal obstruction by stenting. As the safety profile of stenting for colorectal cancer is well characterised, only Serious Adverse Events (SAEs) experienced during treatment will require expedited reporting, Adverse events which do not fulfil the criteria of 'serious' will be collected via the appropriate CReST2 CRFs.

8.6.2. Serious Adverse Events

AEs defined as serious and which require reporting as an SAE should be reported on a **CReST2** SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE.

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be sent by fax to the **CReST2** trial office as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE form to:

0121 415 8871 or 0121 415 9136

On receipt, the Trial Office will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt. If confirmation of receipt is not received within 1 working day then the site must contact the **CReST2** Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the Site File.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the **CReST2** Trial Office and a copy kept in the Site File.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.6.3. Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form.

8.7. Reporting Procedure – Trials Office

On receipt the **CReST2** Trial Office will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the TMF.

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

8.8. Reporting to the Research Ethics Committee

8.8.1. Unexpected and Related Serious Adverse Events

The CReST2 Trial Office will report all events categorised as Unexpected and Related SAEs to the REC within 15 days of being made aware of the event.

A copy is also sent to the University of Birmingham Research Governance Team and the Sponsor's office at the time of sending out the Unexpected and Related Serious Adverse Event.

8.8.2. Other safety issues identified during the course of the trial

The REC will be notified immediately if a significant safety issue is identified during the course of the trial.

The University of Birmingham Research Governance Team and the Sponsor's Office will also be informed at the time that the REC is informed.

8.9. Reporting to Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be stored in the Site File.

8.10. Data Monitoring Committee

The independent Data Monitoring and Ethics Committee (DMEC) will review all SAEs.

9. Data Handling and Record Keeping

9.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Source data is kept as part of the participants' medical notes generated and is generally kept and maintained at site. Within **CReST2**, this includes the CT scans. The CRFs will not be the source for any data.

In addition, for this trial, Quality of Life and patient-completed questionnaires will be recorded at various time points; this source data will be kept in a locked filing cabinet within the colorectal team office at BCTU.

9.2. CRF Completion

Data reported on each Case Report Form will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete CRFs will adhere to Good Clinical Practice guidelines and will be trained on the requirements of data capture as per protocol, including:

- *Date format and partial dates*
- *Rounding conventions*
- *Trial-specific interpretation of data fields*
- *Entry requirements for concomitant medications* (generic or brand names)
- *Which forms to complete and when*
- *What to do in certain scenarios, for example when a subject withdraws from the trial*
- *Missing/incomplete data*
- *Completing SAE forms and reporting SAEs*
- *Protocol and GCP non-compliances*

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Where applicable for the trial this will be evidenced by the signature of the site's Principal Investigator on the CRF.

Data collection within the **CReST2** trial is via paper CRFs. The completed originals will be submitted to the Trial Office and a copy filed in the Investigator Site File; this also applies to the QoL and patient completed questionnaires.

9.3. Data Management

An analyst programmer will build and maintain a bespoke, secure application for the **CReST2** trial data. This application will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically undertaken on small sub-samples. All data merging programs and macros will be tested prior to acceptance of the system. This application will contain data management capabilities such as, for example, generating reminders for missing data. This application will also contain a system to allow randomisation to the **CReST2** trial 24 hours a day, and 365 days a year.

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate different individuals who would be chiefly responsible for local co-ordination of either the clinical, policy or administrative aspects of the **CReST2** study.

A data manager will be employed within BCTU to assist the coordinator with the collection of CRFs and to resolve any inconsistencies in the data. The data manager will be responsible for reconciling the information supplied by the informatics department following their monthly interrogation of the

HES records including identifying which hospital services have been used by the trial participants in the previous month with the correct patient record.

A statistician from BCTU will perform all statistical analyses for the DMEC and other reports, as well as providing all analyses for the final report.

The health economist will collaborate with the statistician and data manager to ensure the data management system is appropriate with regards to allowing the collection of suitable data to perform appropriate economic analyses. A research assistant will perform the cost-effectiveness analysis.

A research nurse will be employed and based with the Chief Investigator. This coordinating research nurse will help facilitate recruitment by performing site initiation visits and helping to promote the study throughout the UK.

9.4. Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years.

No trial documents will be destroyed without prior written approval from the **CReST2** Trial Office.

10. Quality control and quality assurance

10.1. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV to the **CReST2** Trial Office. All members of the site research team will also be required to sign a site delegation log. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed GCP training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The **CReST2** Trial Office must be informed immediately of any change in the site research team.

10.2. Monitoring

Monitoring of this trial will be to ensure compliance with Good Clinical Practice. A risk proportionate approach to the initiation, management and monitoring of the trial will be adopted (as per the MRC/DH/MHRA Joint Project: Risk adapted Approaches to the Management of Clinical Trials) and outlined in the study-specific risk assessment.

10.2.1. On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow **CReST2** trial staff access to source documents as requested.

10.2.2. Central Monitoring

The Trials Office will be in regular contact with the site research team to check on progress and address any queries they may have. The Trials Office will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or for clarification of any inconsistencies or discrepancies.

10.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are requested to notify the CReST2 Trial Office of any inspections.

10.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with the trial or the protocol relating to the trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, the Trial Steering Committee, the Sponsors, and the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC

11. End of Trial Definition

The first 12 months of recruitment will form the internal feasibility study to test the viability of **CReST2**. This internal feasibility will assess the rate of recruitment over 12 months to determine if it is feasible for **CReST2** to continue or whether it should be halted.

At the end of the feasibility phase, the Trial Management Group will prepare a report for the TSC and DMEC detailing recruitment information and data gained from screening logs. The TSC and DMC will be asked to make recommendations on whether they think that recruitment to the feasibility study has shown that progression to a full phase III study is justifiable.

Data from the feasibility phase will not be unblinded or reported to the Trial Management Group but carried forward – if the study continues – to the full trial. If the study is found to be feasible, then the study will move seamlessly into a full phase III study.

The end of trial will be 12 months after the last data capture. The Trials Office will notify the REC and the participating sites that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

12. Statistical Considerations

12.1. Definition of Outcome Measures

12.1.1. Primary outcome measures

See section 2.2.

12.1.2. Secondary outcome measures/exploratory endpoints

See section 2.2.

12.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those treated with a covered stent versus those treated with an uncovered stent. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol violation. For all major outcome measures, summary statistics and differences between groups, e.g. relative risks will be presented, with 95% confidence intervals and p-values from two-sided tests also given. Outcomes will be adjusted for the minimisation variables listed in section 6.2 where possible. No adjustment for multiple comparisons will be made. Due to the inherent potential for bias, any per-protocol analyses carried out will not, irrespective of any differences to the primary analyses, supplant the planned primary analyses.

12.2.1. Primary Outcome Measures

The first co-primary endpoint in **CReST2** is Quality of Life at 3 months measured using the QLQ-C30 global health score. The questionnaire will be scored by the original validated method. An independent two-sample t-test will be used to compare the treatment arms at three months post-randomisation. Estimates of differences between the two arms, and the corresponding 95% confidence intervals, will be reported.

The second co-primary endpoint in **CReST2** is stent patency at 6 months. A logrank analysis, censoring at prior death, will be used to estimate the probability of the stent still being in place at 6 months.

Regression models may be constructed in order to take into account the minimisation variables.

12.2.2. Secondary Outcome Measures

Data regarding complications from stenting will be collected at 30 days (short term), 1-3 months (intermediate term) and 3-12 months post-stent (long term). The incidence of stent related complications (e.g. perforation, blockage, migration) will be compared between treatment arms at each timepoint, both overall and for each complication separately, using a chi squared test. Additionally the overall complication rate will be compared using the same method. All complications will be included together in this analysis.

Overall survival will be compared between treatment arms using survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons. Results will be expressed as hazard ratios with 95% confidence intervals.

The proportion of patients requiring stoma formation will be compared between treatment arms using a chi squared test. Duration of stoma will be analysed using Kaplan-Meier methods. Other exploratory analyses may be performed. Results obtained from any exploratory analyses will be treated as hypothesis-generating only.

If covered stents are found to be an effective approach for management of obstructing colorectal cancer in patients treated with palliative intent in terms of increased quality of life and extended survival, then this may have potentially important cost implications for the health care sector. For example, patients may suffer from reduced complications and may experience the reduced probability of progressing to surgery and to stoma formation, all of which could lead to reduced resource usage.

The aim of the economic evaluation is to determine the cost-effectiveness of implementing covered stents for patients presenting with obstructing colorectal cancer treated with palliative intent that are in need of a stent, compared to implementing an uncovered stent. This cost-effectiveness analysis will take the form of a cost-utility analysis in which the primary outcome measure will be the cost per quality adjusted life year (QALY) which utilizes quality of life estimates collected from patients using EQ-5DL during the trial alongside patient survival. The results for the secondary outcome of cost per case of complications averted will also be considered.

Cost Data collection
Data collection will be undertaken prospectively for all patients in the RCT in order to inform the cost component of the cost-effectiveness analysis. The main resource uses monitored during trial which will be collected by the trial staff and will include the following:

- Resource use associated with implementing a stent (e.g. the stent, inpatient days, additional medication, staff time)
- Outpatient appointments
- Chemotherapy
- Stoma care (procedures, treatment, staff time)
- Costs related to complications

The costs of the resource usage will be informed by the most up to date editions of NHS reference costs and the Unit Costs of Health & Social Care with a health care provider perspective being adopted.

Analysis
A model based analysis will be conducted following the conclusion of the data collection during the RCT. A decision analytic model will be used to allow the extrapolation of the cost and effectiveness parameters beyond the data observed during the trial and will adopt a life-time time horizon. The patient pathways will be informed by the data collected during the RCT.
The results of the economic analysis will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. Simple and probabilistic sensitivity analysis will be used to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used and to consider the broader issue of the generalisability of the results obtained from the economic evaluation.

12.2.3. Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see section 5.2). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

12.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. Full details will be included in the Statistical Analysis Plan.

12.2.5. Planned Randomisation Methodology

See section 5.2.

12.3. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (serious adverse events) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in section 13.5.

The first 12 months of recruitment will form the internal feasibility study to test the viability of **CReST2**. This internal feasibility will assess the rate of recruitment over the previous 12 months to determine if it is feasible for **CReST2** to continue or should be halted due to futility.
The final decision on whether **CReST2** is halted will rest with members of the TSC.

12.4. Planned Final Analyses

The recruitment rate to **CReST2** will be closely monitored during the first 12 months after the study commences. At the one year time point recruitment will be reviewed to ensure that it is sufficient to attain the target sample size within the stated time frame.

Data in **CReST2** is collected at the timepoints shown below:

Outcome Measure	**Timepoint (post-stent)**						
	Baseline	30 days	3 months	6 months	12 months	18 months	24 months
QoL: QLQ-C30, QLQ-C29, EQ-5DL	**x**	**X**	**x**	**x**	**x**	**x**	**x**
Stent complications		**X**	**x**	**x**	**x**		
Stoma formation		**X**	**x**	**x**	**x**		
Endoscopic re-intervention			**x**	**x**	**x**	**x**	**x**
Resource Usage							
Adverse events	**Monitor throughout study**						
Survival					**x**		

The primary analysis for the study will occur once all participants have completed the 6 month assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including the 6 month assessment and no further. Longer term data from later time-points will be analysed separately once participants have completed the corresponding assessments.

12.5. Power Calculations

Norman and colleagues conducted a systematic review of the literature relating to the minimally important difference for health-related Quality of Life instruments. They conclude that in most circumstances, the threshold of discrimination for changes in health-related quality of life for chronic disease appears to be approximately half a SD (7).

Cohen also devised criteria for estimating Minimally Important Differences in health-related Quality of Life; he expressed differences as an effect size – the average change divided by the baseline SD. He stated that in the context of comparing group averages, a small effect size was 0.2, a medium was 0.5 and a large effect size was 0.8 (8).

The sample size for **CReST2** is based on two co-primary outcomes: QLQ-C30 global health score at 3 months, and stent patency at 6 months. For Quality of Life, a 0.5 SD difference between groups would be clinically meaningful. For stent patency, the expected patency rate in the control arm is 30% and an improvement to 50% in the patients receiving a covered stent would be clinically meaningful.

To detect a difference of 0.5 SD in Quality of Life and an improvement in stent patency from 30% to 50% between groups using the standard methods (comparing means and comparing proportions with

continuity correction respectively) with 90% power and a type I error rate of 2.5% to account for the multiple comparisons, a total of 157 participants per group will need to be randomised, 314 in total. Assuming and adjusting for a 10% loss to follow-up/ drop-out rate, 350 participants will need to be recruited.

Larger Quality of Life effect sizes have been reported in acute conditions (9), but we consider that at 3 months post stenting, the clinical circumstances are most like those of a chronic disease. It may be possible to investigate smaller effect sizes, e.g. 0.4 SD, but this would depend on clinicians' enthusiasm for recruitment to the trial as the sample size would need to be increased appropriately – whilst adhering to the same timeframe. Any decision on reducing the effect size would only be taken after seeking advice from the independent TSC.

13. Trial Organisational Structure

Professor Hill (Chief Investigator) will have overall responsibility for the conduct of **CReST2**. The trial will be managed within the Coloproctology trials team at the University of Birmingham Clinical Trials Unit. The trials team lead will oversee the management of the study and a dedicated trial coordinator will be appointed with responsibility for the day-to-day management of the project.

Together with Professor Gray, the lead statistician for the trial, the trials staff and Professor Hill will meet on a monthly basis to discuss trial progress and management. The larger Trial Management Group, consisting of all of the co-applicants, will meet on a three-monthly basis. Professor Kay will be the Lead Radiologist for the study, and along with Professor Hill, will review all serious adverse events on an ongoing basis. The TMG will also be responsible for drafting the final report and submission for publication.

13.1. Sponsor

CReST2 will be sponsored by Central Manchester University Hospitals NHS Foundation Trust.

13.2. Trials Office

The **CReST2** Trial Office is at the University of Birmingham Clinical Trials Unit.

13.3. Trial Management Group

The Trial Management Group includes the individuals responsible for the day-to-day management of the **CReST2** trial (listed at the front of this protocol). The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

13.4. Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the **CReST2** trial. A Trial Steering Committee (TSC) will be convened for the study. This will comprise an independent chair, a patient representative, a further independent clinician and a person with significant experience of running clinical trials. Members of the TMG (CI, trial coordinator, statistician and clinical co-applicants) will also participate.

The TSC will meet every 12 months to review trial procedures and recruitment. They will review and act upon the recommendations of the DMEC. The TSC will monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

13.5. Data Monitoring Committee

Unblinded data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together

with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet annually unless there is a specific reason to amend the schedule.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the **CReST2** Trial Steering Committee who will convey the findings of the DMC to theTrial Management Group.

The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

CReST2 does have an initial 12 month feasibility phase and the stop / go criteria are set out in Section 11.

13.6. Finance

CReST2 is an investigator-initiated and investigator-led trial funded by the National Institute for Health Research Health Technology Assessment programme (Call 14/28 Covered versus uncovered self-expanding metallic bowel stents).

The CReST2 TMG is working with stent manufacturers to secure stent supply for the study at a reduced cost.

CReST2 should not involve any extra treatment costs for participating hospital Trusts. No additional follow-up visits or investigations are required other than those which would normally be required as part of standard clinical care.

14. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Guidelines for Good Clinical Practice (GCP)).

Before any participants are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

15. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

Participants will be identified using only their unique trial identification number and date of birth on the Case Report Forms and on correspondence between the CReST2 Trials Office and the participating

site. However, the Randomisation Form will also collect patient intitials, NHS/CHI Number and Hospital Number. Participants will give their explicit consent for the Trial Office to hold this information. Participants will give their explicit consent for the Trials Office to be sent a copy of their consent form. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the CReST2 Trials Office (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

The Trials Office will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer, i.e. The Health Informatics Team at The University Hospitals of Birmingham NHS Foundation Trust. Representatives of the **CReST2** Trials Office and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

16. Insurance and Indemnity

Central Manchester University Hospitals NHS Foundation Trust has in place Clinical Trials indemnity coverage for this trial which provides cover to the NHS Foundation Trust for harm which comes about through the Trust's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the Trust's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

Central Manchester University Hospitals NHS Foundation Trust is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

17. Publication Policy

The results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the **CReST2** Trial Management Group and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed and authorisation given in writing by the **CReST2** Trial Management Group. Final manuscripts must be submitted to the **CReST2** Trial Management Group in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of Central Manchester University Hospitals NHS Foundation Trust, the University of Birmingham Clinical Trials Unit and the NIHR HTA.

18. Reference List

1. National Bowel Cancer Audit Report (2015) hscic.gov.uk/catalogue/PUB195000/nati-clin-audi-supp-prog-bowel-canc-2015.pdf

2. Zhang Y, Shi J, Shi B, Song CY, Xie WF, Chen YX (2012). Comparison of efficacy between uncovered and covered self-expanding metallic stents in malignant large bowel obstruction: a systematic review and meta-analysis. *Colorectal Disease* 14(7): e367-e374.

3. Choi JH, Lee YJ, Kim ES, Choi JH, Cho KB, Park KS, Jang BK, Chung WJ, Hwang JS (2013). Covered self-expandable metal stents are more associated with complications in the management of malignant colorectal obstruction. *Surg Endosc*. 9:3220-7.

4. Yang Z, Wu Q, Wang F, Ye X, Qi X, Fan D (2013). A systematic review and meta-analysis of randomised trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract. *Int J Med Sci*. Apr 27;10(7):825-35.

5. Park S, Cheon JH, Park JJ et al (2010) Comparison of efficacies between stents for malignant colorectal obstruction: a randomized prospective study. *Gastrointest Endosc,* 72:304-1.

6. Park JK, Lee MS, Ko BM, Kim HK, Kim YJ, Choi HJ, Hong SJ, Ryu CB, Moon JH, Kim JO, Cho JY, Lee JS (2011) Outcome of palliative self-expanding metal stent placement in malignant colorectal obstruction according to stent type and manufacturer. *Surg Endosc*. Apr;25(4):1293-9.

7. Norman GR, Sloan JA, Wyrwich K (2003). Interpretation of Changes in Health Related Quality of Life - the remarkable universality of half a standard deviation. *Medical Care* 41:582-592.

8. Cohen J. (1969) Statistical power analysis for the behavioural sciences. London: Academic Press:1969

9. Bedard G, Zeng L, Zhang L, Lauzon N, Holden L, Tsao M, Danjoux C, Barnes E, Sahgal A,Poon M, Chow E (2014). Minimal important differences in the EORTC QLQ-C30 in patients with advanced cancer. *Asia-Pac J Clin Oncol* 10: 109-117.

19. Abbreviations and Definitions:

Term	Description
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
Related Event	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event (SAE)	An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator** Comments: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious
Unexpected and Related Event	An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event	The type of event that is not listed in the protocol as an expected occurrence.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
Trials Office	The team of people, including the Chief Investigator, responsible for the overall management and coordination of the trial.