TRIAL PROTOCOL

CReST2

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

V2.0 02-Jan-2024

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 seven-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 the 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.

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ISRCTN number	54834267
REC reference number	17/NE/0027

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

PROTOCOL DEVELOPMENT AND SIGN OFF

Protocol contributors
This protocol was written by the CReST2 Trial Management Group.

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment no.	Date of amendment	Protocol version no.	Type of amendment	Summary of amendment
1	21 Sep 2017	1.0	Substantial	Introduction of patient facing letters
2		2.0	Substantial	Update to trial end date, covid-19 considerations, patient confidentiality and withdrawal implications, update to oversight committee details.

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Funder's reference number	14/28/02
Funder's call:	14/28: Covered versus uncovered self-expanding metal bowel stents
This protocol was written in response to a commissioned call from the NIHR HTA programme (14/28). The funder of the trial will have no role in the trial design, data collection, data analysis or data interpretation. This study is funded by the NIHR HTA programme as referenced above. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.	

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial Name:	CReST2
Protocol Version Number:	2.0
Protocol Version Date:	02-Jan-2024
CI Name:	Professor James Hill
Trial Role:	Chief Investigator
Signature:	
Date:	

Sponsor statement

Manchester University NHS Foundation Trust is the sponsor for CReST2 and maintains oversight of protocol development. The signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Compliance statement

This protocol describes the CReST 2 trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the CReST 2 trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act (2018) and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof.

Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name: Protocol version number: Protocol version date:	CReST2: ColoRectal Stenting Trial 2 Version: __ __ __ __ / __ __ / __ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __/ __ __/ __ __ __ __

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Trial Summary

CReST2: ColoRectal 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 being managed with a palliative intent but treated 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 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 of 20 NHS sites across the UK.

Outcome Measures

***Primary*:**

- The Quality of Life at 3 months measured using the QLQ-C30 global health score (Question 29)
- 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 3-6 months (long term) post-stent
- Stent related complication rates of patients undergoing chemotherapy
- The cumulative frequency of stoma formation in each arm
- Overall survival at 6 months
- Quality of Life at 3 months measured using the QLQ-CR29 Disease Specific Module for Colorectal Cancer
- Cost effectiveness using the outcome measure of cost per quality adjusted life year.

Key Eligibility Criteria

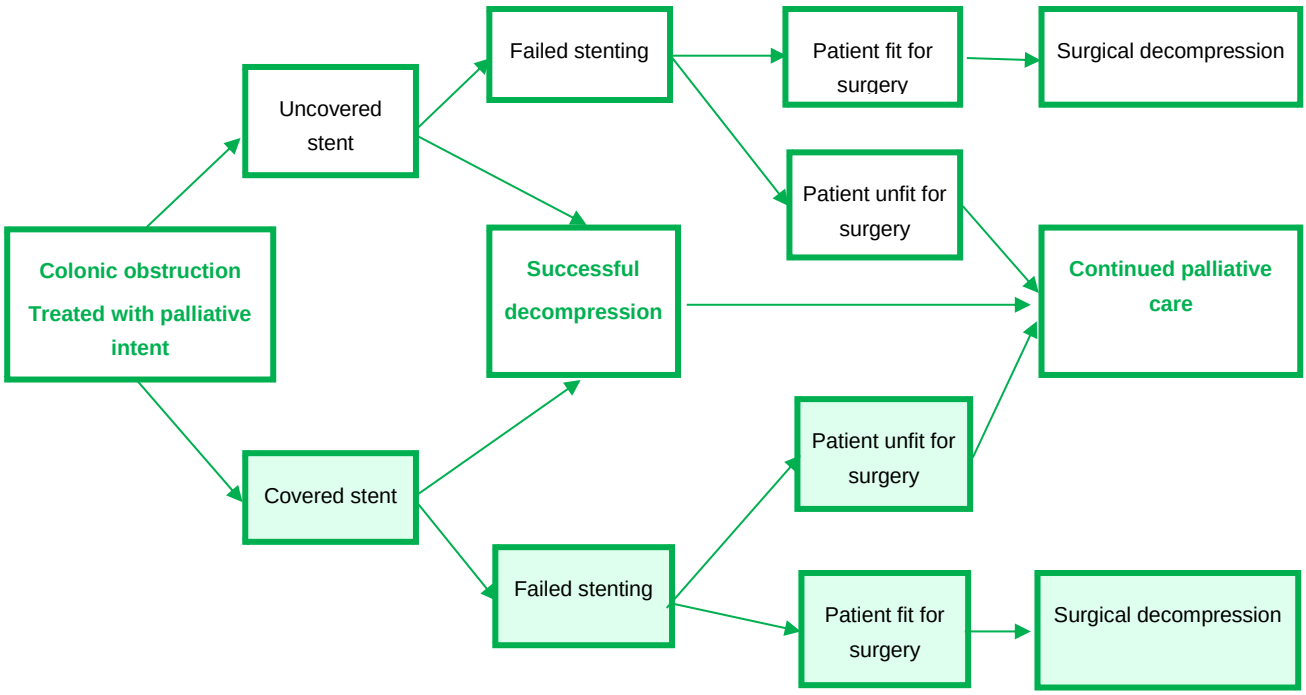
Patients aged 16 and over, who are not pregnant and who present with colonic obstruction and radiological features consistent with a carcinoma which requires decompression. These patients will have colorectal cancer and the stenting procedure will be considered to be a palliative measure for the relief 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



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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 of 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 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 as well as maximising the quality of life of people suffering from bowel obstruction arising from colorectal cancer.

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 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 [6]. In this trial of 151 patients with malignant colorectal obstruction, 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 paucity of 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 relieving bowel obstruction arising from colorectal cancer. 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 by the trial office. The trial office will reveal the nature of the stent inserted should there be a valid clinical or safety need. See Section 6.4.
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 defined in Section 2.2 of 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. For CReST2, stents with any covering will be classed as covered stents. The stent should 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 relieving obstruction in palliative patients with obstructing colonic cancer, i.e. 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 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.

The aim of the internal feasibility trial is to assess if recruitment to the randomised intervention is feasible and to assess clinician equipoise at 12 months after the start of recruitment to the internal feasibility study

2.2. Internal Feasibility

2.2.1. Internal Feasibility Aim

The first 12 months of recruitment will form the internal feasibility study. The aim of this study is to assess the rate of recruitment at 12 months post recruitment of the first patient 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 Stop/Go Criteria

The feasibility of the trial will be assessed at 12 months post start of recruitment. Recruitment to CReST2 commenced in June 2017.

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 (CRFs) will be measured during the feasibility trial. At the end of the feasibility phase the return rate of scheduled, site completed, 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 mean 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 initial phase study has shown that undertaking 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 if:

1. The Quality of Life for palliative colorectal cancer patients requiring a stent is dependent on whether the stent is covered or uncovered
2. The efficacy of the stent is 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 (successful stent placement and relief of obstruction) are different between covered and uncovered stents
2. If the incidence of stent-related complications (perforation, re-obstruction, 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 at 6 months
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 measured using the QLQ-C30 global health score and compared with the baseline.

2. Stent patency (stent still *in situ)* post-stenting (time to failure by logrank analysis) at 6 months.

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 3-6 months (long term) post-stent
3. Stent related complication rates of patients on chemotherapy in each arm
4. The cumulative frequency of stoma formation in each arm
5. Overall survival at 6 months
6. Quality of Life at 3 months measured using the QLQ-CR29 Disease Specific Module for Colorectal Cancer
7. Cost effectiveness using the outcome measure of cost per quality adjusted life year.

3. Trial Design and Setting

3.1. Trial Design

CReST2 is a multi-centre, randomised controlled trial with an initial 12-month feasibility phase. The trial is double-blinded, therefore, only the trial office and the clinical specialist 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.
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 and HSCNI centres. Participating centres must have placed at least 30 stents for the treatment of obstructing colorectal cancer, with participating individual surgeons, radiologists or endoscopists, having placed at least 10.
However, 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 CReST2 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 CRFs. These Principal Investigators were contacted about the CReST2 study and 24 sites indicated their support.

3.3. Identifying patients

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.

3.4. Risk Assessment

All clinical trials can be considered to involve an element of risk. In accordance with BCTU operating procedures, this trial has been risk assessed to clarify any risks relating uniquely to this trial. This risk assessment concluded that as both types of stents compared in CReST2. are used as part of standard care no additional tests or visits are required. Thus there are no additional risks to patients from the study intervention.
The main risk to data validity is low return rates for the Quality of Life Questionnaires arising from the palliative nature of the population in this study. The importance of obtaining completed Quality of Life questionnaires is emphasised at Site Initiation Visits and sites are provided with guidelines designed to maximise questionnaire return. A consideration is also made for site nurses to contact participants prior to the questionnaire due date,
Due to the design of the study associated risks were identified with inadvertent site unblinding of the nature of the stent placed. Stages of the procedure where unblinding is a risk are highlighted at site initiations visits. All CRFs contain text which warms sites not to include the stent type. In addition, the person who received the allocation cannot complete or sign off stent follow up forms. Adherence to blinding will be monitored at BCTU and any non-compliance followed up with the site.
A possible risk identified during 2020/21 is that of the covid-19 pandemic.

Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: Type A = No higher than the risk of standard medical care

3.5. COVID-19 considerations

CReST2 has been extensively reviewed for any impact caused by the COVID-19 pandemic. Members of the Trial Management Group (TMG) agreed that, due to the urgent nature of the patient population, COVID-19 offers zero barrier to the selection and recruitment of CReST2 participants. The consent process also remains unchanged, and is treated the same as normal NHS consent for the stenting procedure. In addition, there is no change to the pathway of the patient whilst in hospital, as the patients experience from admission to discharge is no different to if they were not recruited to CReST2. Patient follow up is also not affected, as clinical follow up questions found on the stent follow up case report form are taken from hospital records, and do not require direct contact with the patient. Patient quality of life questionnaires are sent directly to patients from the CReST2 trial office, or from the site where applicable, with pre-addressed return envelopes. These assessments were made with approval from the independent Trial Steering and Data Monitoring and Ethics Committees, the Funder, and Sponsor.

4. Eligibility

4.1. Inclusion criteria

- Patients presenting with obstructing colorectal cancer which is to be managed with palliative intent, where this includes patients with one or more of the following:
    - unresectable local disease
    - unresectable metastatic disease
    - considered unfit for surgery
- Patients aged 16 years and over
- Patients able and willing to give written, informed consent.

4.2. 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)
- Patients who are pregnant at the time of randomisation

A positive test of COVID-19 at entry, or during the study, is not an exclusion from CReST2.

4.3. Co-enrolment

Patients who are participating in other clinical trials are not automatically excluded from CReST2, but sites must contact the Trial Office prior to randomising the patient.
The site should also contact the CReST2 Trial Office if a CReST2 participant is being considered for another clinical trial.

5. Consent

It will be the responsibility of the local Investigator or their delegate 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. The discussion should include explanation of the Quality of Life component and the requirement for patients to complete questionnaires at regular intervals.
Investigators 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. Medically qualified doctors and Research Nurses can discuss the trial with a patient, but they must be delegated this task by the Principal Investigator. This must be documented in the Signature and Delegation of Duties Log.
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. Only medically qualified doctors who have been delegated this task can take consent and sign the consent 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 the 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 continued participation in the study 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 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.

6. Enrolment and Randomisation

6.1. Enrolment and screening

Patients may be identified through routine and emergency settings as outlined in Section 3.3. Sites should ensure there are methods in place to identify and refer potentially eligible patients in both of these settings.
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 at the time of assessment, and found to have an obstruction which it is believed would be resolved by stenting, the person will be eligible to participate in CReST2, providing other eligibility criteria are met.
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
Written consent will be obtained from the participant as described in Section 5 and this will be confirmed by the trials office during randomisation.

6.2. 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 receive either a covered stent or an uncovered stent. A minimisation algorithm will be used to ensure balance in the treatment allocation over the following variables:

1. Age (those aged <=70; those aged >70)
2. WHO performance status (See Section 21 for definition of categories)
3. Tumour site (i.e. ascending colon; hepatic flexure; transverse colon, splenic flexure, descending colon, sigmoid, rectosigmoid and proximal rectum)
4. The primary indication for palliation (unresectable local disease, unresectable metastatic or considered unfit for surgery)

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability 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 local Investigator Site File (ISF). A copy of the screening log for the previous month should be sent to the Trial Office monthly. The CReST2 Patient Recruitment and Identification Log and CReST2 Participant Screening/Enrolment Log should be held in strict confidence.
If the participant has agreed to participate in the CReST2 study then, the participant's GP will be notified using the REC approved CReST2 GP Letter.

6.2.1. Randomising a patient to CReST2

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)

After informed consent has been received and eligibility confirmed, the participant can be randomised into the trial. Randomisation notepads are provided in the CReST2 ISF and should be used to collate the necessary information prior to randomisation.
Randomisation can be undertaken directly by the site using a secure online randomisation system based at the Birmingham Clinical Trials Unit (BCTU). 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. Sites must also receive training in use of the online randomisation system. The system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.
A Freephone telephone randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00, except for bank holidays and University of Birmingham closed days.
After all the necessary details have been provided, the patient's unique trial number will be generated and this will be confirmed by email to the PI and site administrative contact. As CReST2 is a blinded study, the confirmation email will contain the trial number only. The person inserting the stent will be informed of the allocation by a separate email.

6.3. Blinding of treatment allocation

CReST2 is a double-blinded study. Therefore, only the trial office and the clinical specialist 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.
Following randomisation, the clinician inserting the stent will be informed by email of the allocation by the trial office. To minimise the risk of other personnel being informed of the allocation (e.g. if the person inserting the stent changes), randomisation should take place as close to the day of stenting as possible.
The person placing the stent will be asked only to record in the patient's notes and endoscopy report that they placed the stent as part of the CReST2 trial, and not the type of 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 (see Section 6.4).
In order to monitor compliance with the treatment allocation, the clinical specialist inserting the stent will be asked to complete a Compliance Form and return this to the Trial Office immediately following the stent insertion procedure. Sites are also instructed to include the stent packaging label on this form, so that a record of the stent placed is held at the trial office. This form will be supplied with a pre-paid envelope to ensure no other members of the trial team see the allocation.

To minimise bias, the person inserting the stent should not complete the patient's trial related follow up.

6.4. Unblinding procedure

Unblinding is permissible but should only be undertaken for an urgent clinical need or patient safety issue.

There will be an online system to allow for emergency unblinding. Access to this function will be strictly controlled and be available only to the PI and a very limited number of clinicians.
The unblinding information will be released on a per patient basis, and an email will be generated to alert the CReST2 Trial Office, the Chief Investigator, local Principal Investigator and CReST2 Statistician that unblinding has taken place.
The reason for any unblinding will be investigated. If unblinding is found to have been unnecessary this will constitute a Serious Breach.
If it becomes necessary to unblind a patient, then members of the site research team should remain blinded where possible to the nature of the stent placed, subject to clinical need. Unblinded participants will remain in the trial and continue with trial follow-up assessments.

7. Trial intervention

7.1. Treatment

The stents being used in CReST2 are all 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 TMG. This will allow practitioners inserting stents to use the stent type that they are most familiar with. A list of stents approved for use within the CReST2 trial has been collated by the CReST2 TMG and is provided to participating sites.

7.2. Compliance with allocation

Compliance with treatment allocation will be monitored by the CReST2 Trial Office by comparing the nature of the stent recorded as being inserted on the CReST2 Compliance Form with that stated in the randomisation allocation. As a further check, the label from the stent packaging should be included with the Compliance Form. To maintain the blind this form must only be completed by the person who inserted the stent and returned immediately following stent insertion to the CReST2 Trial Office in the pre-paid envelope provided.

7.3. 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 the Stent Follow-Up CRF or the SAE CRF (or both)). The nature of any re-intervention will be at the discretion of the treating clinician who will use their skill, clinical knowledge and experience to determine the most appropriate treatment. Immediate technical failures where the stent was not successfully placed should be reported on the Stent Insertion CRF. Clinicians may use any type of stent (i.e. covered or uncovered) if the patient requires further stent procedures.

7.4. Stent Supply and Storage

7.4.1. Treatment Supplies

Participating Trusts will be responsible for purchasing stents using their usual procurement procedures. For CReST2, covered stents are those which have are covered to any degree. The stents will be stored as per local practice and made available for use dependent upon allocation. To maintain blinding, personnel involved in maintaining stent supplies and retrieving the allocated stents for use must not be involved in patient follow up.

7.4.2. Packaging and Labelling

Prior to use, the stents will be kept in their original manufacturers packaging. After placement, the label from the stent packaging should be placed on the Compliance Form as further confirmation of the stent used.

8. Trial procedures and assessments

8.1. Trial procedures

8.1.1. Prior to randomisation

Patients in whom a large bowel obstruction is suspected will undergo a standard CT scan of their abdomen and pelvis. Some patients may also have a contrast enema and some may also have an endoscopy. These are not mandated by the protocol and are undertaken as required by clinical practice.

8.1.2. Confirmation of eligibility

The CT scan will confirm obstruction and staging of the primary and secondary disease. Patients with a symptomatic stricture due to colorectal cancer and who are identified as probably having incurable/unresectable disease, and/or patients assessed as being unfit for major surgery but in whom stenting is seen as a viable treatment are eligible to participate in CReST2.

8.1.3. Informed consent

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.
Patients will be encouraged to discuss the trial with a member of the CReST2 research team at site. Research nurses can discuss the trial, but not take informed consent. Following a discussion during which the potential participant will be encouraged to ask questionsThe the participant will then be given a suitable period of time to consider participation in the CReST2 trial. . See Section 5 for details of obtaining informed consent.
Those who agree to participate in CReST2 will sign and date a consent form in the presence of a member of the CReST2 research team. Only medically qualified doctors who have been delegated this task can take consent. The doctor must also sign and date the 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.

8.1.4. Baseline data

Baseline data are collected on the Randomisation Notepad. All questions must be answered before randomising the patient. In addition, the patient will complete the Baseline Quality of Life Questionnaire.
The patient can then be randomised following the procedures outlined in Section 6.

8.1.5. Stent procedure

CReST2 is a blinded study, therefore only the specialist undertaking stenting will know the allocation (covered or uncovered stent).
Approved types of both 'covered' and 'uncovered' stents will be available in the radiology suite. The clinical specialist who receive the allocation will retrieve the appropriate type of stent (i.e. covered or uncovered) from the theatre supply.
This stent should 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 as many people as possible remain blinded to the type of stent inserted.
All patients will have an x-ray to confirm the stent has opened at the time of stent placement. If x-rays are taken later (e.g. the following day) to check stent placement and/or its expansion, these should not be viewed by staff blinded to treatment allocation.

8.1.6. Patient follow up

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 using the centre's standard care pathways.
Sites will provide data to the Trial Office using CRFs. See Sections 8.2 and 8.3 for details of assessments.
Patient identifiers and personal information such as age, gender and date of recruitment will be transferred to the Leeds Institute of Health Economics at University of Leeds for linkage with Hospital Episode Statistics (HES) to provide additional follow-up data.
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.
The results data from the CReST2 trial will be owned by the University of Birmingham.

8.2. Schedule of assessments

Assessments/outcome data collection	TIMEPOINT								
			TIME POST RANDOMISATION						
	Baseline	Stent insertion	24 hours	30 days	3 months	6 months	12 months	18 months	24 months
Eligibility check	X								
Informed Consent	X								
Randomisation	X								
Procedure (Stent Insertion)		X							
Patient Follow Up: *Trial specific visits are not required. Data can be collected from patient records.*									
Stent complications			X	X	X	X	X		X
Reinterventions			X	X	X	X	X		X
Survival			X	X	X	X	X		X
Chemotherapy details							X		
Quality of Life Questionnaires	X			X	X	X	X	X	X
Resource usage		X	X	X	X	X	X	X	X
Adverse Events	**Monitored throughout**								

8.3. Summary of assessments

CRFs are completed at Baseline, following the stent insertion procedure and at the time-points indicated in the Schedule of Assessments (Section 8.2).

8.3.1. Baseline forms

The Randomisation Notepad is completed once eligibility has been confirmed and patient has provided informed consent. This form documents stratification variables and other information required to enter the patient into the trial.

8.3.2. Stent insertion procedure

The following forms are completed following stent procedure:

- The Compliance Form is completed immediately following stent procedure to confirm that the allocated type of stent has been used; this form can only be completed by the person inserting the stent
- The Stent Insertion Form is completed immediately following stent procedure to collect data on technical success and stent procedure
- The Discharge Form is completed upon discharge from hospital following the stent procedure and collects data on number of bed days

8.3.3. Follow up forms

Data on stent patency, stent complications and survival are collected from the participating site at the following time-points: Follow up data are collected for all participants, even where stent insertion has been unsuccessful, or subsequently fails.

- 24 hours (for complications from stent insertion up to 24 hours post procedure)
- 30 days (for all complications from 25 hours to 30 days post procedure)
- 3 months (for all complications from 31 days to 3 months post procedure)
- 6 months (for all complications from 3 months to 6 months post procedure, plus data on any Chemotherapy during trial)
- 12 months (all events from 6 months to 12 months)
- 24 months (long term follow up).

At these time-points, details of each event, including the date of event and any re-intervention will be recorded.

Data will also be used in the Cost Effectiveness analysis.
Further information on re-interventions will be collected via Intraoperative Form and/or Stent Insertion Form.

8.3.4. Quality of Life Questionnaires

Quality of Life data (co-primary outcome measure) will be collected via patient completed QLQ-C30 questionnaires. Participants will also complete the QLQ-CR29 questionnaire to inform secondary outcomes. The EQ-5D-5L questionnaire is also completed to inform Health Economics Analysis. The Baseline Questionnaire will be completed following consent, but before randomisation.
It is intended that subsequent forms will be posted to patients by the Trial Office following discussion with site staff. The consent form includes permission for the Trial Office to hold patient addresses for this purpose. As Quality of Life is a co-primary outcome, collection of these data are essential. Sites will be provided with guidelines on obtaining questionnaires including initial discussion with patients and obtaining follow up data.
Questionnaires are completed at the time-points indicated in the Schedule of Assessments.

8.4. Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.
Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.
Participants found to be ineligible post randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.
CReST2 does not involve ongoing trial treatment or trial specific visits, so the types of withdrawal possible are:

- The participant does not wish to complete Quality of Life Questionnaires, but is willing for their data from hospital records to be collected for the CReST2 trial. In addition, they are willing for information maintained by NHS Digital or its equivalent in the devolved nations to be collected.
- The participant does not wish to complete Quality of Life Questionnaires, but is willing for any data from hospital records to be collected for the CReST2 trial. The participant also does not wish for the collection of any information maintained by NHS Digital or its equivalent in the devolved nations. No additional Quality of Life Questionnaires will be sent to the participant from the date of withdrawal, and the participant will not be included in exports received from NHS Digital or its equivalent in the devolved nations.
- The participant would like to withdraw from further participation and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis). Any data collected until the date of withdrawal will continue to be processed.
- The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).. Any data collected until the date of withdrawal will be excluded from all analyses performed.

The details of withdrawal (date, reason [if known] and type of withdrawal) should be clearly documented in the source data and provided to the CReST2 Trials Office.

9. Adverse Event Reporting

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) within CReST2 will be in accordance with the UK Policy Framework for Health and Social Care Research [7], the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions (Section 21). 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.

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, re-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 treatment plan and the outcome of the event.

9.2. Adverse Events (AE)

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.
CReST2 will collect AEs related to stent complications, including:

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

These events should be recorded on the relevant Case Report Form (CRF). However, as they are key outcomes for CReST2, these events should also be reported as SAEs (See section 9.3).

9.3. Serious Adverse Events (SAE)

All events which meet the definition of serious will be collected and recorded in the participant notes. In addition, events which require reporting as SAEs for CReST2 will be reported to the trials office immediately and within 24 hours of the site being made aware of the event.
An SAE is defined as an untoward event which:

- Is fatal or immediately life threatening
- Requires or prolongs hospitalisation
- Results in persistent or significant disability or incapacity
- Constitutes a congenital anomaly or birth defect
- Otherwise considered medically significant by the investigator
- In addition, for CReST2 stent related complications must be reported as SAEs, this includes:
    - Failure to deploy the stent
    - Perforation
    - Migration
    - Re-obstruction

9.3.1. Exceptions to SAE reporting

For CReST2, the following events do not require reporting on an SAE form:

- Pre-planned or elective hospital admissions (unless for stent related procedures)
- Admission to hospital or other institution for general care not associated with trial intervention, e.g. infections (unless from perforation), falls, progression of disease

However, these events should still be recorded by the trial team in the participant's notes and, if required, within the relevant CRF.

9.4. Monitoring pregnancies for potential Serious Adverse Events

Women who are pregnant at the time of randomisation will not be eligible to participate in CReST2. Women of reproductive age who are otherwise eligible should receive a pregnancy test.

The risk of congenital anomalies or birth defects in the offspring of participants who subsequently become pregnant is negligible. In addition, the age profile and health status of CReST2 participants means that the risk of becoming pregnant is very low. Therefore, there will be no monitoring of pregnancies in CReST2.

9.5. Reporting period

The reporting period will commence when the participant gives consent to participate in CReST2.
The reporting period for each participant will cease 6 months after the insertion or attempted insertion of the first 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 six-month post-stenting quality of life questionnaire.

9.6. Reporting Procedure: Site

9.6.1. Adverse Events

As the safety profile of stenting for colorectal cancer is well characterised, only Serious Adverse Events (SAEs), as defined in Section 9.3, 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.

9.6.2. Serious Adverse Events

AEs defined as serious (see Section 9.3) and which require reporting as an SAE should be reported on a CReST2 SAE Form. When completing the form, the PI or delegate will be asked to define the causality and the severity of the AE.
On becoming aware that a participant has experienced an SAE, the PI (or delegate) must complete, date and sign an SAE Form. The form should be sent by fax or email 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, or email to CReST2@trials.bham.ac.uk

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 one 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 Principal Investigator (PI) (or a medically qualified delegate) the PI (or delegate) will be required to assess the SAE for causality and severity and countersign the original SAE Form. 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.

9.6.3. 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.

9.7. Reporting Procedure: Trials Office

On receipt of an SAE, the CReST2 Trial Office will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt within one 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 by the Trial Office, seriousness and causality will be determined independently by a Clinical Coordinator. For CReST2, the Clinical Coordinator is the Chief Investigator or member(s) of the TMG delegated this task by the Chief Investigator.
An SAE judged by the 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.
A summary of all SAEs will be sent to the Sponsor.

9.8. Reporting to the Research Ethics Committee

9.8.1. 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.
Details of any Unexpected and Related SAEs will also be sent to the University of Birmingham's Research Governance Team and the Sponsor's office at the time of informing the REC.

9.8.2. 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 made aware of any safety concerns at the time that the REC is informed.

9.9. 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 will be stored in the Site File.

9.10. Data Monitoring Committee

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

10. Data Handling and Record Keeping

10.1. 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 partly that obtained from the participants' medical notes, hospital records and other reports and procedures. These are generally kept and maintained at the local site. Within CReST2, this source data also includes the relevant scans and their reports. Completed CRFs will not form the source for any data.
In addition, for this trial, Source Data will also include any patient questionnaires. These data will be kept in a locked filing cabinet within the colorectal team office at BCTU.

10.2. CRF Completion

Data reported on each CRF 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
- 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 PI to ensure that the CRF has been completed correctly and that the data it contains are accurate. This will be evidenced by the signature of the site's PI or delegate on the CRF. Where the PI has also performed stent insertion, they cannot complete or sign off CRFs for patient follow up. Therefore, the task of completing and signing off CRFs may be delegated to appropriately qualified and trained personnel.
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.
A list of Self-Evident Corrections (SECs) will be compiled. These are corrections to non-critical data items on site completed CRFs which can be made by Trials Office staff. Such changes will only be made once the site Principal Investigator has confirmed agreement by signing Declaration Form. Any SECs made to forms will be documented and a copy sent to the site.

10.3. Data Management

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.

An analyst programmer from Birmingham Clinical Trials Unit 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.
A data manager will be employed within BCTU to assist the trial coordinator with the collection of CRFs and to resolve any inconsistencies in the data.

Health Economics analysis will be performed by the HES team at University of Leeds using data received Hospitals Episodes and Statistics records, when linked, will identify whether patients have used any NHS services including the number of hospital outpatient visits, A&E attendances and inpatient admissions. This data will be used to calculate a Health Economics cost effectiveness analysis.
Linkage to ONS records will also be provided detailing date and the cause of death as listed on the death certificate of any participants in the CReST2 study

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.
The results data from the CReST2 trial will be owned by the University of Birmingham.

10.4. 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.

10.5. Data Security

University of Birmingham (UoB0 has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.
The Trial Database System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.
- Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.
- System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented by the Programming Team.
- System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational processes: the data will be processed and stored within BCTU.
- System audit: the system will benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

11. Quality control and quality assurance

11.1. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the relevant agreements and supply a signed and dated CV and GCP certificate to the CReST2 Trial Office.
The Delegation of Duties Log lists the duties which the PI has delegated to each member of the research team. By signing the Delegation of Duties log, the PI confirms that the member of staff is qualified to undertake these duties.
All members of the research team must be qualified by education, training or experience to undertake trial related duties delegated to them. Signed and dated current CVs for all staff

listed on the delegation log must be sent to the CReST2 Trial Office as evidence of education and training prior to the person undertaking any study procedure.
All those undertaking informed consent should be GCP trained. Following the latest HRA guidance regarding the requirements for GCP training [8] individuals who only perform their usual tasks will not be required to hold a current GCP certificate. However, all staff must observe the principles of Good Clinical Practice. Therefore, BCTU strongly recommends that all staff undertake GCP training.
Prior to commencing recruitment all sites will undergo a process of initiation. 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 (ISF) 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, and a copy of the updated Delegation Log sent to the Trials Office

11.2. Monitoring

Monitoring of this trial will be to ensure compliance with Good Clinical Practice Guidelines (GCP) [9]. A risk proportionate approach to the initiation, management and monitoring of the trial will be adopted [10] and outlined in the study-specific risk assessment.

11.2.1. 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.

11.2.2. 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 CRFs 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.

11.3. Audit and Inspection

The Principal Investigator (PI) 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 PI will comply with these visits and any required follow up. Sites are requested to notify the CReST2 Trial Office of any inspections.

11.4. 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 (TMG), the Trial Steering Committee (TSC), the Sponsor, and the REC. A copy of the relevant documents will also be sent to the University of Birmingham's Clinical Research Compliance Team at the time of reporting to the REC.

12. 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 study will assess the mean rate of recruitment over 12 months to determine if CReST2 is viable or 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 6 months after the last data capture, including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. 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.

13. Statistical Considerations

13.1. Sample Size

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 [11].

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 [12].

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 the loss of follow up continues at its current rate of 30%, 350 participants will need to be recruited.

Larger Quality of Life effect sizes have been reported in acute conditions [13], 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.

13.2. 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.

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 (covered vs. uncovered stent) to which they were randomised irrespective of compliance or other protocol violation. For all major outcome measures, appropriate 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. A Bonferroni correction has been applied, reducing alpha from 0.05 to 0.025 to account for any increase in the risk of type I error that may be associated with having co-primary outcome measures (see section 13.1). 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.

13.2.1. Primary Outcome Measures

The first co-primary endpoint in CReST2 is Quality of Life at 3 months post-randomisation, measured using the QLQ-C30 global health score. The questionnaire will be scored by the original validated method. A linear regression model will be constructed to compare the treatment arms at 3 months post-randomisation, adjusting for the minimisation variables listed in section 6.2. 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 post-randomisation. A logrank analysis will be used to estimate the unadjusted probability of the stent still being in place at 6 months. Patients who exit the trial (e.g. death, total withdrawal of consent) will be censored at the point of exit. An adjusted analysis will be undertaken by fitting a Cox Proportional Hazards model to take into account the minimisation variables, with a test to ensure that the proportional hazards assumption is not violated. Hazard ratios and corresponding 95% confidence intervals will be reported.

13.2.2. Secondary Outcome Measures

Data regarding complications from stenting will be collected at 30 days (short term), 1-3 months (intermediate term) and 3-6 months post-stent (long term). The incidence of stent related complications (e.g. perforation, re-obstruction, migration) will be compared between treatment arms at each timepoint, both overall and for each complication separately, using a chi squared test or Fisher's exact test if necessary. 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 QLQ-CR29 Disease Specific Module for Colorectal Cancer will be scored by the original validated measure.

The proportion of patients requiring stoma formation will be compared between treatment arms using a chi squared test or Fisher's exact test if necessary. Other exploratory analyses may be performed. Results obtained from any exploratory analyses will be treated as hypothesis-generating only.

Cost-Effectiveness

If covered stents are found to be an effective approach for the 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-5D-5L during the trial alongside patient survival. The results for the secondary outcome of cost per case of complications averted will also be considered.

Data collection will be undertaken prospectively for all patients in the trial in order to inform the cost component of the cost-effectiveness analysis. The resource use collected will include:

- 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.
A model based analysis will be conducted following the conclusion of the data collection during the trial. 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 trial.
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.

13.2.3. 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.

13.2.4. 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.

13.3. 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 14.5
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.

13.4. 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.
A summary of data collection points is given in Section 8.1 and 8.2.
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.

14. Trial Organisational Structure

As Chief Investigator, Professor James Hill will have overall responsibility for the conduct of the CReST2 trial. The trial will be managed within the Coloproctology trials team at Birmingham Clinical Trials Unit, which sits within the University of Birmingham. 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.
The Trials Management Group will meet on a monthly basis to discuss trial progress and management. The TMG will also be responsible for drafting the final report and submission for publication.

14.1. Sponsor

CReST2 is sponsored by Manchester University NHS Foundation Trust.

14.2. Trials Office

The CReST2 Trial Office is part of the University of Birmingham’s Clinical Trials Unit.

14.3. Trial Management Group

The TMG includes the comprises 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. The TMG will meet sufficiently frequently to fulfil its function.

14.4. Trial Steering Committee

A Trial Steering Committee (TSC) will be convened for the study. The role of the TSC is to provide the overall supervision of the CReST2 trial. This committee 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) will also participate in TSC meetings.
The TSC will meet at least every 12 months to review trial procedures and recruitment. 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.

14.5. 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 [14]. The DMC will meet at least annually unless there is a specific reason to amend the schedule.

Additional meetings may be called if required, e.g. if recruitment is much faster than anticipated. At their discretion, the DMC may 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 TSC who will convey the findings of the DMC to the Trial 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 has an initial 12-month feasibility phase and the stop / go criteria are set out in Section 2.2.

14.6. Finance

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

15. 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, and amendments [15]

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care [7], the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018) and the Guidelines for Good Clinical Practice (GCP) [9].

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

16. Confidentiality and Data Protection

Personal data and sensitive 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 2018 (and subsequent amendments).
Participants will be identified using only their unique trial identification number and date of birth on the CRFs and on correspondence between the CReST2 Trials Office and the participating site. However, the Randomisation Form will also collect patient initials, 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, which includes patient name. This will be used to perform in-house monitoring of the consent process. Patients also consent to the Trial Office holding their postal address, collected on the Postal Address Form, for the purpose of sending Quality of Life Questionnaires. All forms which have patient identifiable data (consent form, randomisation form and address form) will be stored separately to other CRFs in the CReST2 trials office.
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.
The data will be held on a secure SSL server within the University of Birmingham. A small number of 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 who need this access in order to deliver the study outcomes.
Representatives of the CReST2 Trials Office and Sponsor may be required to have access to participants' notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.
Patients have the right to withdraw at any time, as detailed in Section 8.4.

17. Insurance and Indemnity

Manchester University 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.

Manchester University 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.

18. Access to final dataset

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the final data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third part who withholds their consent, of the BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in the absence of the CI) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG) and independent Trial Steering Committee (TSC).

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

19. Publication Policy

The results of this trial will be submitted for publication in a peer reviewed journal and will be published in the name of the collaborative group.
A meeting will be held after the end of the trial to allow discussion of the main results among the collaborators prior to publication. The success of the trial depends entirely on the wholehearted collaboration of a large number of doctors, nurses and researchers. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the trial. A writing committee will be convened to produce publications on behalf of the CReST2 Collaborating Group.
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. It will also be necessary to submit any publications to NIHR for approval.
Authors must acknowledge that the trial was performed with the support of Manchester University NHS Foundation Trust, the University of Birmingham Clinical Trials Unit and the NIHR HTA.

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21. 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.

22. WHO Performance Status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead