HART

Hughes Abdominal Repair Trial

ABDOMINAL WALL CLOSURE TECHNIQUES to REDUCE THE INCIDENCE of INCISIONAL HERNIAS

HART

Study Protocol

Hughes Abdominal Repair Trial
Abdominal wall closure techniques to reduce the incidence of incisional hernias: A multi-centre pragmatic randomised trial

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Signature page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal requirements.

Chief Investigator:

Signed: _____ Date: _____

Name: _____

Title: _____

Statistician:

Signed: _____ Date: _____

Name: _____

Title: _____

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Abbreviations

ACCEPT	Acceptance Checklist for Clinical Effectiveness Pilot Trials
CEAC	Cost-Effectiveness Acceptability Curves
COGNATE	Cancer of Oesophagus or Gastricus - New Assessment of Technology of Endosonography (RCT)
CONTINT	CONTinuous versus INTerrupted abdominal wall closure after emergency midline laparotomy
CRC	Colorectal Cancer
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CT	Computerised Tomography
CTU	Clinical Trials Unit
DMC	Data Management Committee
DVT	Deep Vein Thrombosis
FACT-C	Functional Assessment of Cancer Therapy - Colorectal
HART	Hughes Abdominal Repair Trial (RCT)
ICER	Incremental Cost-Effectiveness Ratio
IH	Incisional Hernia
LRTI	Lower Respiratory Tract Infection
MI	Myocardial Infarction
NRCM	National Research Collaborative Meeting (surgical)
NICE	National Institute for Health and Care Excellence
PACS	Picture Archiving and Communications System
PE	Pulmonary Embolus
PROM	Patient-Reported Outcome Measure
QALY	Quality Adjusted Life Year
QoL	Quality of Life
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RES	Research Ethics Service
SF12 or SF36	Short Form 12 or 36 (quality of life questionnaires)
SOPs	Standard Operating Procedures
SSI	Surgical Site Infection
STITCH	Suture Techniques to reduce the Incidence of The inCisional Hernia (RCT)
STU	Swansea Trials Unit
TDG	Trial Development Group
TMG	Trial Management Group
UHW	University Hospital of Wales
UTI	Urinary Tract Infection
WBRG	Welsh Barbers Research Group
WWORTH	West Wales Organisation for Rigorous Trials in Health

Protocol Synopsis

Title	Hughes Abdominal Repair Trial: A pragmatic multi centre randomised clinical trial comparing the Hughes Repair with Mass Closure in the prevention of Incisional Repair.
Summary	A surgical study comparing the rates of incisional hernia one year following one of two closure methods for abdominal surgery.
Primary Objective	The primary objective is to compare the incidence of incisional hernias over one year from colorectal cancer surgery between the Hughes and standard mass closure.
Primary Outcome	The primary outcome is the incidence of incisional hernias over one year as assessed by clinical examination of the abdomen.
Secondary Objectives	To compare quality of life over one year following colorectal cancer surgery between the Hughes and standard mass closure (the principal secondary aim). To evaluate the cost-effectiveness of the Hughes Repair relative to standard mass closure over one year. To test whether the Hughes Repair reduces the incidence of postoperative 'burst abdomen' (complete abdominal wound dehiscence) between the Hughes and standard mass closure by day 30. To identify and characterise patient and surgical factors which increase the risk of developing incisional hernias. To estimate prevalence of incisional hernias at one year following surgery for colorectal cancer in patients receiving Hughes or standard mass closure. To compare the quality of life between patients with incisional hernias and those without incisional hernias in both arms of the study over one year.
Population	The study will recruit up to 830 adult patients undergoing abdominal surgery (for colorectal cancer) who are suitable to receive Hughes repair or mass closure. Patients can have had abdominal surgery previously.
Phase	N/A
Number of sites	Feasibility phase: single site Pilot phase: up to 8 (Welsh) sites Main phase: approximately 20 (UK) sites
Description of intervention	Abdominal wound of the control group will be closed by standard procedure, mass closure. The experimental group will be closed

	using the Hughes repair.
Study Duration	Analysis will compare data from the pilot and main study phases (800 patients). From point of first patient randomised into the pilot study to primary endpoint analysis will take about four years.
Subject Participation Duration	From point of consent, the intervention would usually take place within a few days, with primary endpoint data collected at one year. However, annual review for 5 years post intervention is planned, conditional on funding.

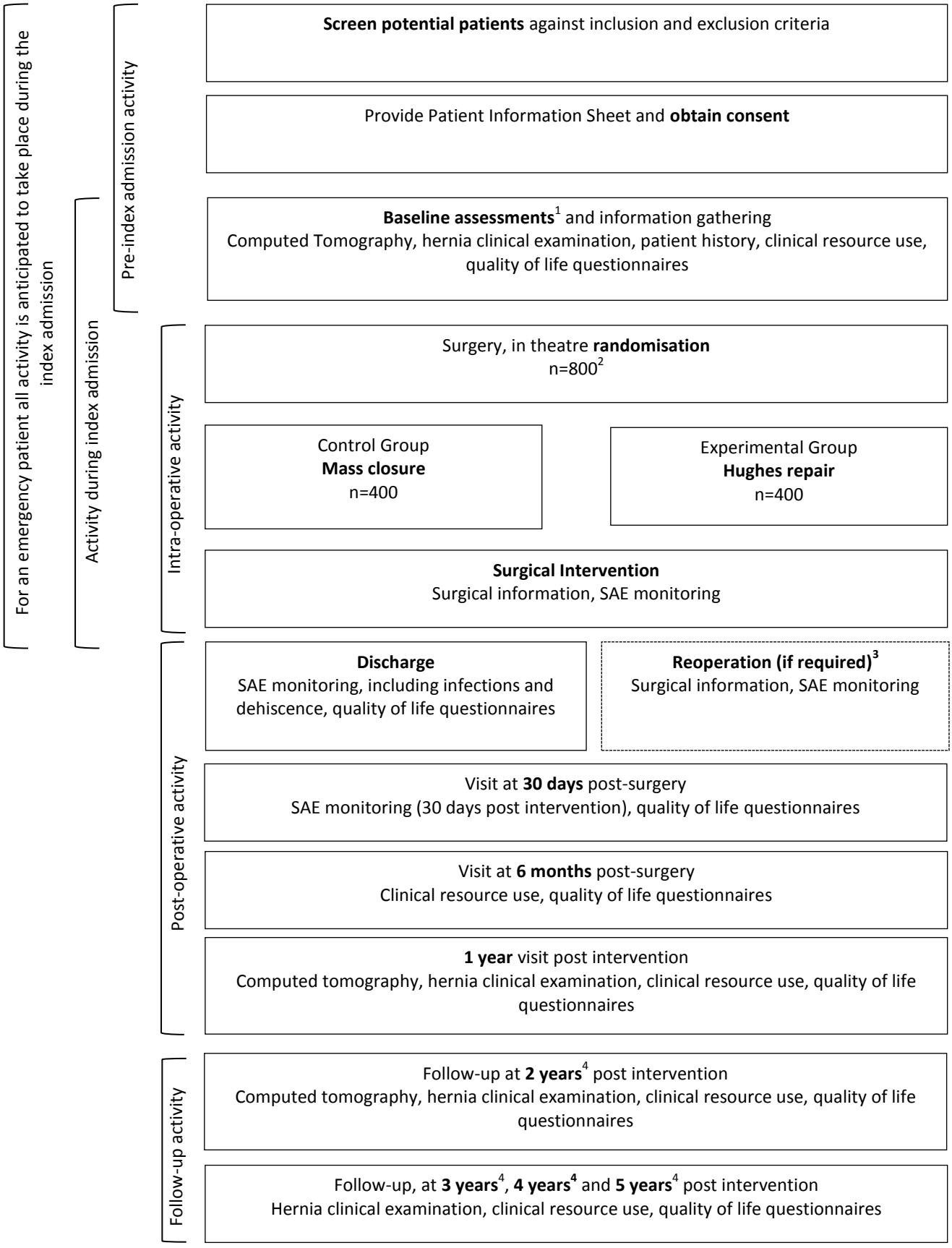

Figure 1. Schematic of Study Design

[1]Can occur at index admission or prior to this. [2]Number of patient in pilot and main study, does not include the 30 feasibility patients. [3]Reoperation prior to discharge [4]Pending further funding. Visit windows are described in the patient schedule in Table 3.

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1. Background

1.1. Literature review

More than 2000 patients are diagnosed with colorectal cancer in Wales each year. Most undergo surgery as part of their treatment. The incidence of complications following colorectal cancer surgery is high [1] and has a significant impact on patients' lives in the form of readmissions, extended length of stay, increased morbidity and reduced quality of life.

Incisional hernias are "abdominal wall gaps around postoperative scars, perceptible or palpable by clinical examination or imaging" [2, 3]. They are common complications of midline closure following major abdominal surgery, including colorectal surgery, and cause significant morbidity, impaired quality of life and increased cost [4]. The standard technique for abdominal closure is 'mass closure' (closing all layers of the abdominal wall, excluding the skin), usually with non-absorbable sutures, although 'slow-resorbing' sutures such as polydioxanone (PDS) are also widely used [5]. The Hughes Repair is an alternative technique of abdominal wall closure using 'near and far' sutures, which has reportedly reduced wound complications substantially as the sutures lie across the rectus sheath [6]. Initially designed to repair incisional hernias [7], this technique is increasingly used for primary closure [8].

The incidence of incisional hernias varies considerably depending on the type of operation undertaken and other surgical and patient variables. Furthermore, it is well recognised that incisional hernias may only become clinically apparent two or more years after surgery [9, 10]. Hence failure to review patients over a prolonged time period may lead to underestimation of the prevalence of abdominal wall incisional hernias. As a result of these factors, the reported incidence of incisional hernias ranges widely; from 8.6% to 33% following open colorectal surgery, and from 4.7% to 24.3% following laparoscopic colorectal surgery [11-14].

The long term results of incisional hernia repair are disappointing. The two main surgical options for fixing these hernias are suture repair (using an elaborate suture method to re- close the abdominal wall) or mesh repair (suture closure reinforced by a synthetic mesh), yet recurrence rates are as high as 12% to 54% and 2% to 36% respectively [15, 16]. Incisional hernia repair may also lead to serious complications such as entero-cutaneous fistulae, bowel obstruction or chronic pain, which have an even greater impact on quality of life. Given such disappointing results from corrective surgery, the search for preventative measures, including better primary surgical

techniques, is of vital importance.

Many factors contribute to the pathogenesis of incisional hernias by impairing wound healing. These include diabetes mellitus [17], obesity [17, 18], cachexia [19], age greater than 45 [18], male sex [18, 20], history of COPD [19, 21] post- menopausal status [22], history of abdominal aortic aneurysm [23], anaemia [19], history of smoking [20] and certain medications (e.g. corticosteroids) [24]. Most of these are outside the surgeons' control. The only modifiable factor identified which has a substantial impact on incisional hernia rates is the surgical technique, and material used, to close the abdominal wall musculo-fascial layer.

There have been many studies to identify the best technique for abdominal wall closure, yet there is still uncertainty about this. For example, the meta-analyses by Hodgeson *et al* [8], Van Riet *et al* [16] and Weiland *et al* [25] concluded that non-absorbable sutures reduce incisional hernia risk, whilst the more recent meta-analysis by Diener *et al* [15] showed that absorbable sutures were associated with a lower risk. Such a discrepancy may be due in part to different inclusion or exclusion criteria. Furthermore, most studies included in these meta-analyses recruited small numbers of patients and lacked sufficient power to detect statistically significant differences between groups [15].

More recent work has focused on different techniques used to close the abdominal wall. For example, the STITCH trial [26] is a Dutch multicentre, randomised controlled trial (currently recruiting patients) comparing small stitch continuous sutures with (large stitch) standard mass closure. The CONTINT RCT, also currently recruiting, is comparing continuous with interrupted sutures in closing midline incisions after emergency laparotomy [27].

As part of our preliminary investigation into the burden of IHs, we have estimated the cost of repairing all IHs in the lead applicant's hospital over the financial year 2011-12. Eighty-five patients were admitted for IH repair. Thirty-three patients are currently on waiting lists to undergo repair. Five operations were cancelled owing to bed shortages or co-morbidity preventing operation. The 67 primary repairs and 14 recurrent repairs (1 patient underwent 2 recurrent repairs in the study period) used 40 half-day theatre sessions over 12 months. In effect IHs use one theatre session a week. The total cost of IH repairs over 1 year, including the cost of outpatient appointments, radiological investigations (ultrasound and computed tomography), overnight hospital stay and the cost of open and laparoscopic surgical repair, was about £225,000. Extrapolating these local results to the UK as a whole, IH repairs costs the NHS in excess of £5.5million per year.

The effects of IHs on patients' QoL, subsequent hospital admissions, and reoperations (both elective and emergency) have seen little research. One exception to this is the recent prospective study by van Ramshorst et al. [28], which has shown that more than 80% of IHs are symptomatic, and affect QoL as assessed prospectively by the SF36 tool. Patients with IHs had lower scores on the SF36 components of physical function and body image.

The eponymously titled 'Hughes Repair' (Professor Les Hughes, 1932-2011 [29]), also known as the "far-and-near" or "Cardiff Repair" [30] is based on the application of a simple technique grounded on sound surgical principles as first described by Professor Hughes. It combines a standard mass closure with a series of horizontal and two vertical mattress sutures within a single suture, theoretically distributing the load along the incision length as well as across it (see figure 1 and 2). The principles are:

- to ensure, by palpation, that only sound normal tissues are used for the repair
- to use graduated tension for easy approximation and
- use a monofilament Nylon suture, which has the advantage of slipping easily through tissues to create a pulley system [10].

The Hughes Repair has been demonstrated to be as effective as the standard mesh repair in treating patients with incisional hernias [7]. It is also used for closing abdomens when patients are at high risk of IHs, after the rare occurrence of a "burst abdomen" (where the closure falls apart about 10 days after the operation), and after laparostomy [31]. This proposed trial aims to ascertain if this technique can be used as primary prevention for incisional hernia formation. In addition it will provide valuable information on the aetiology of incisional hernia with an objective, radiological assessment of the formation of incisional hernia that has not been used previously in this type of study.

After multiple studies, including meta-analyses, the outcome of midline laparotomy mass closure, with respect to the rates of incisional hernia formation, has essentially not improved. Therefore the use of alternative techniques of midline abdominal wall closure [26] should be considered, which might reinforce the surgical wound and notably reduce the incidence of incisional hernias.

The proposed research presented in this protocol aims to assess an alternative wound closure method to prevent or reduce the occurrence of a common but potentially serious complication: incisional hernia, with the subsequent improvement in quality of life for

patients. Feasibility studies suggest that the Hughes Repair is simple to learn and to use in clinical practice, and has substantial potential to reduce the incidence of incisional hernias after surgery. The Hughes Repair does not require any additional materials compared to standard mass closure. Furthermore, follow-up for patients who have been treated for colorectal cancer already includes outpatient assessment, including examination of the abdominal scar, and regular CT imaging of the abdomen. This trial therefore does not require any expensive or dangerous intervention, additional outpatient appointments, or extra abdominal imaging, but simply utilises pre-existing services to ascertain incisional hernia rates. The proposed trial is applicable to all colorectal surgery departments and has the potential to improve surgical practice, reduce morbidity and result in financial savings to the NHS.

The Hughes Abdominal Repair Trial (HART) has many potential benefits, including clinical, economic and epidemiological. Reducing the incidence of incisional hernia by altering the abdominal wall closure technique after colorectal surgery is likely to reduce the expense of subsequent surgical repair. It would improve quality of life for such patients. Whether the Hughes Repair alters incisional hernia rates or not, this trial will assess the epidemiology and risk factors for incisional hernia across the UK.

1.2.Rationale

The study aims to assess the potential of an alternative wound closure method to prevent incisional hernias; a common and sometimes serious complication of abdominal surgery.

The study will recruit colorectal cancer patients who are due surgical treatment. The patient's treatment will follow its standard course, except at point of wound closure where they will be randomised to a Hughes or mass closure.

Colorectal cancer patients undergo clinical examinations and a computed tomography (CT) scan prior to surgery. Following surgery, as part of their standard treatment, they will have further annual clinical examinations and CT scans. The study will use these standard assessments to monitor for incisional hernias.

The patients will also be monitored for their quality of life, which may be improved with reduced incisional hernias.

In addition, the trial will assess the epidemiology of, and risk factors for, incisional hernia.

1.3. Hypothesis

The null hypothesis states that there is no difference in the rates of incisional hernias over

one year in patients having midline abdominal wall closure following elective or emergency colorectal cancer surgery – between the Hughes Repair and standard mass closure.

The alternative hypothesis states that the Hughes Repair alters the incidence of incisional hernia over one year in patients having midline abdominal wall closure incisions following elective or emergency colorectal cancer surgery when compared with standard mass closure.

2. Aims, objectives and outcomes

The study is split into three phases; feasibility, pilot and main.

The feasibility phase aims to demonstrate the validity of the study documentation and provide preliminary data for 30 patients. The data will inform the pilot and main phase of the study. The DMC will review the feasibility data and study processes against a predetermined set of criteria and determine whether the study can continue into the pilot phase. Feasibility data will not contribute to the final analysis of the study.

The pilot phase aims to demonstrate that the study documentation and processes are sufficient for implementation at other centres. A total of 80 patients will be recruited into the pilot phase at up to 8 sites (one of which is the feasibility site). The DMC will review the pilot data and provide guidance on study continuation or termination.

The ACCEPT criteria [32] will be applied to the feasibility and pilot phase.

The main phase will recruit 720 patients from around 20 sites, totaling 800 patients between the pilot and main phase of the study.

Both the pilot and main phase trial data will contribute to the study analysis.

2.1. Objectives

2.1.1. Primary objective

The primary objective is to compare the incidence of incisional hernias over one year from colorectal cancer surgery between the Hughes and standard mass closure.

2.1.2. Secondary objectives

The secondary objectives are:

a. To compare quality of life over one year following colorectal cancer surgery between

the Hughes and standard mass closure (the principal secondary aim).

b. To evaluate the cost-effectiveness of the Hughes Repair relative to standard mass closure over the first year.
c. To test whether the Hughes Repair reduces the incidence of postoperative 'burst abdomen' (complete abdominal wound dehiscence) between the Hughes and standard mass closure by day 30.
d. To identify and characterise patient and surgical factors which increase the risk of developing incisional hernias.
e. To estimate prevalence of incisional hernias at one year following surgery for colorectal cancer in patients receiving Hughes or standard mass closure.
f. To compare the quality of life between patients with incisional hernias and those without incisional hernias over one year.

2.1.3. Tertiary objectives

Conditional on funding to follow patients from one to five years, the tertiary objectives are:

a. To assess the prevalence of clinically detectable incisional hernias at five years from surgery.
b. To evaluate the effect of the Hughes Repair on participants' quality of life over five years from surgery.
c. To evaluate the cost-effectiveness of the Hughes Repair relative to standard mass closure over 5 years from the perspective of health and social care.
d. To compare the sensitivity and specificity of CT image identification of incisional hernia over 2 years with those of clinical diagnosis over 2 to 5 years following surgery.
e. To compare the quality of life between patients with incisional hernias and those without incisional hernias in both arms of the study over 5 years.

2.2.Outcomes

2.2.1. Primary outcome

The primary outcome is the incidence of incisional hernias over one year as assessed by clinical examination of the abdomen.

The clinical presence of a hernia will be assessed either by a surgeon, or a nurse specialist who has received clinical examination training as part of their role. The presence of a hernia can be detected as a reducible, palpable mass, usually with a cough impulse, which may cause the patient discomfort or pain. Each clinical examination should follow the process described in Section 6.2.

2.2.2. Secondary outcomes

The following secondary outcomes will be assessed:

a. Two Quality of Life Patient Reported Outcome Measures (PROMs) will be administered at baseline, 30 days, 6 months and 1 year to assess the differences between the two trial groups. The questionnaires used will be SF-12 [37], a shorter version of the original SF36 [38] and the Functional Analysis of Cancer Therapy – Colorectal (FACT-C) [39].

b. Cost-utility analysis of the Hughes Repair in relation to the mass closure in colorectal cancer patients from the perspective of the NHS will be undertaken.

Information regarding resource use will be collected, focusing on surgery-specific resources including, but not limited to, open or laparoscopic surgery, duration of surgery, suture details, number and type of complications especially IHs and other SAEs, and subsequent use of health and social care.

To measure the subsequent use of health and social care, an existing Client Service Receipt Inventory (CSRI) has been adapted for surgical procedures. A CSRI is a research instrument for collecting data on service use by patients, originally developed for use in Mental Health Services [40]. The unit costs of all these resources will be estimated using published data. Incremental cost-effectiveness ratios (ICER) for IHs avoided will be calculated.

SF-6D utilities will be derived from the responses to SF12 questionnaires and used to estimate changes in patients' QoL over time. They will be combined with survival data to estimate the incremental cost per quality adjusted life year (QALY) gained.

c. Data on the incidence of post-operative 'burst abdomen' or full thickness abdominal wall dehiscence will be collected for up to 30 days post operation, as well as details of any repair surgery and the closing sutures used.

d. Data will be collected regarding patient conditions that are considered to be associated with an increased risk of developing hernias, including but not limited to diabetes and obesity. C-POSSUM (Colorectal - Physiological and Operative Severity Score for Understanding Mortality and Morbidity) scores, developed in 1991 [30] and modified in 2004 [33] to assess risk of mortality and morbidity in patients undergoing colorectal surgery will also be completed. Analysis of these measures will estimate the effect of these factors on IH rates; and whether some patient groups derive greater benefit from the Hughes

Repair than others.

The presence of other hernias (incisional and non-incisional) as identified by clinical examination and CT will also contribute to the risk assessment of developing a midline incisional hernia following abdominal surgery, as some patients may be more susceptible to developing hernias.

Patients who develop post-operative SSIs are also more likely to develop incisional hernias [34]. Unfortunately SSI is one of the common complications of colorectal surgery. Data will be collected for patients developing SSIs in hospital; the SSIs will be classified into superficial, deep (involving muscle or fascia) or confined to an organ or space [35]. On discharge, patients will be asked to keep a diary (as derived from Williams *et al* [36]) for up to 30 days post-surgery to record any community-treated wound-related SSIs. Participants will be asked to return the diary at the 30 day visit or return by post, depending on site preference.

e. The prevalence of incisional hernias at one year as measured by clinical examination will be assessed.

f. The quality of life of patients with or without incisional hernias will be compared over one year. PROMs will be administered at baseline, 30 days, 6 months and 1 year to assess the differences between the two groups.

2.2.3. Tertiary outcomes

Conditional on funding to follow patients from one to five years, tertiary outcomes are as follows:

a. Further clinical imaging will take place at year 2, and clinical examination will continue annually until year 5. Both methods will continue to identify incisional hernias.

b. During the annual review, both SF-12 and FACT-C QoL questionnaires will continue to be completed, and QoL over 5 years will be assessed.

c. SF-6D utilities shall be derived from the responses to SF12 questionnaires, and costs to be derived from the CSRI questionnaires collected on an annual basis.

d. CT scans at one and two years will identify IHs which may be missed by clinical examination at one to five years. They will also validate clinical findings and check for IHs in patients with a large body habitus.

e. The quality of life of patients with or without incisional hernias (as determined by clinical examination) will be compared over 5 years.

Objective		Aim	Measure
Primary		Incidence of hernia at 1 year	Clinical examination
Secondary	a	Quality of life within 1 year	PROMs
	b	Cost effectiveness in the first year	Type of surgery, duration of surgery, CSRI, SF-6D
	c	Complete abdominal wound dehiscence within 30 days of surgery	CRF data and SAE form
	d	Risk factors of developing hernias within one year	Patient history, SSI and other hernia
	e	Prevalence of hernia at 1 year	Clinical examination
	f	Quality of life between hernia and no hernia over 1 year	PROMs
The tertiary objectives relate to data collected up to 5 years			
Tertiary	a	Prevalence of hernia over 5 years	CT and clinical examination
	b	Quality of life over 5 years	PROMS
	c	Cost effectiveness over 5 years	CSRI, SF-6D
	d	Sensitivity and specificity of CT imaging	CT and clinical examination
	e	Quality of life between hernia and no hernia over 5 years	PROMs

Table 1. Summary of study objectives.
Provided is a table outlining all study objectives, and a brief description of the outcome measure. The outcome measures are described briefly within the table, but further information is available in section 2.2.

2.3.Qualitative assessment

A separate protocol will describe the qualitative assessment of a separate group of patients with incisional hernias, assessed as asymptomatic, mild or severe. Also it will explore the views and perceptions of ten healthcare professionals who have experience of the Hughes repair and mass closure techniques.

3. Method

3.1.Design

This is a multi-centre, single (patient) blinded, randomised controlled trial. In addition to patient blinding, the reviewing radiologists and clinical examiners will be blinded, but the closing surgeons will not. The study is split into three phases; feasibility, pilot and main.

Participants will be randomised in equal proportions into one of two arms; to be closed either by a standard mass closure or using a Hughes repair technique. A total of 830 patients will be randomised across all three phases, 415 to each arm.

The pilot and main phase of the study will recruit 800 patients (400 to each arm) and contribute to the main study analysis.

Coordination of the trial will take place by the trial manager based at Cardiff & Vale University Health Board with the Swansea Clinical Trials Unit (formerly WWORTH), Swansea University.

3.2.Study population

The study will identify patients who are due to receive abdominal surgery for the treatment of colorectal cancer. Patients undergoing emergency surgical treatment as well as patients receiving elective surgical treatment will be considered. Patients can have received abdominal surgery previously but not for the colorectal cancer in question. For inclusion in the study, the patient must have a midline incision at least 5cm in length and be considered suitable for standard mass closure. Potentially eligible patients will be logged, and reasons for non-inclusion documented.

3.3.Setting

The feasibility phase is conducted at a single centre; the University Hospital of Wales, Cardiff. The pilot study will roll out to at most 7 further sites in Wales, and the main study will be extended to around another 12 sites in the UK, totaling approximately 20 participating centres. If required to meet recruitment targets, additional sites will be enrolled subject to necessary approvals.

Investigator sites will be selected based on their ability to recruit suitable patients and deliver the study according to protocol.

It is planned that each phase of the study will recruit as outlined in Table 2. For each study phase the DMC will review data and provide guidance on study continuation or termination.

Phase	Number of sites	Number of patients	Recruitment period (planned)
Feasibility	1	30	6 months
Pilot*	Up to 8	80	9 months
Main*	Approximately 20	720	18 months

Table 2. Recruitment plan

*Patient data contributes to final study analysis.

4. Inclusion and exclusion criteria

4.1. Inclusion criteria

At screening

- Patients aged 18 years or older
- Able to give informed consent
- Both standard mass closure and the Hughes repair closure are suitable closing techniques for the patient
- An elective patient for colorectal cancer surgery following full staging investigations including an abdominal CT scan OR an emergency patient with a strong suspicion of colorectal cancer as per CT

At point of surgical closure/ randomisation

- Midline abdominal incision (open or laparoscopic assisted/converted)
- Incision of 5cm or more

4.2. Exclusion criteria

At screening

- Unable to provide informed consent

At point of surgical closure/ randomisation

- Inserting a mesh as part of abdominal closure
- Undergoing musculofascial flap closure of perineal defect in abdomino-perineal wound closure.

5. Study Schedule

In brief, it is anticipated that after screening, consent and surgery, each participant will attend two separate visits during the first year (these may be conducted by phone if required) and have a CT scan and clinical examination at one year post surgery. Data collected at the one year visit will support the primary endpoint.

Conditional on additional funding, patients from the pilot and main phase of the study (not feasibility) will enter a follow-up period involving annual visits for a further four years until year 5 post-operation.

5.1. Screening

Patients identified as having colorectal cancer surgery, either elective (for example via the

Multi Disciplinary Meeting (MDT) or emergency, will be screened against the inclusion and exclusion criteria. Elective patients should be having colorectal cancer surgery, and emergency patients have a strong suspicion of colorectal cancer. Those considered potentially eligible will be provided with the PIS as described in Figure 2. All eligible patients will be logged using a screening log, and reasons for non-inclusion documented.

5.2.Consent

The consent process is shown in Figure 2. Consent will be taken by investigators, after the patient has had ample time to review the PIS and have their questions answered.

Elective: Patients can be given the PIS prior to the admission to hospital for surgery, or at point of admission for surgery, as long as there is ample time to read and review the PIS, and ask questions of the research nurse and/or surgeon, before reaching a decision.

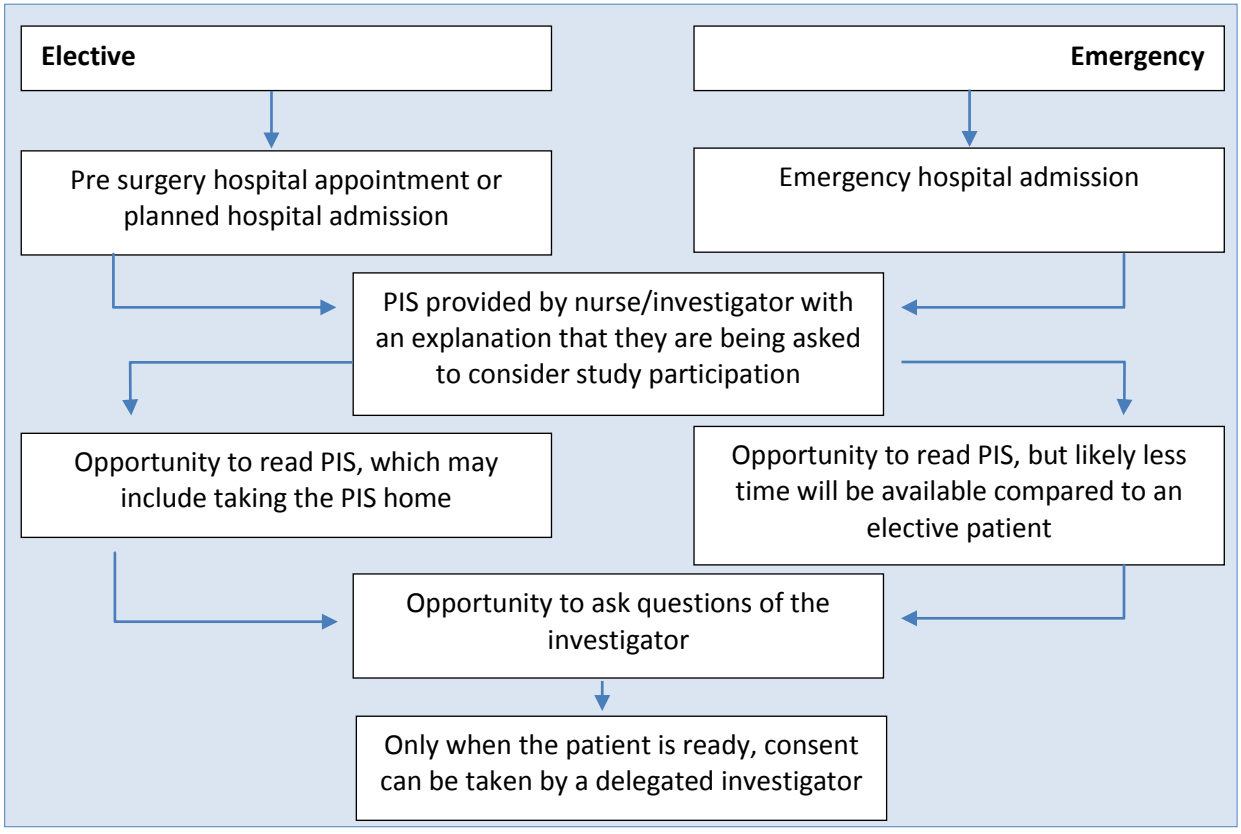

Figure 2 Flow diagram of consent process

The consent process will be slightly different between elective and emergency patients, driven by constraint of time available.

Emergency: Patients undergoing emergency surgery following a preoperative CT scan strongly suggestive of colorectal malignancy will be given the PIS and given adequate time to ask questions while in hospital for the emergency operation. Due to the urgent nature of

the surgery, surgeons should be available to answer questions quickly. Patients will only be approached if their clinical condition allows sufficient time to obtain informed consent. Urgent treatment will not be deferred to obtain informed consent.

5.3.Baseline visit

After the patient has been consented, the baseline visit form will be used by the recruiting site to confirm eligibility and collect data regarding the patient's demography, medical history (including presence of pre-existing hernias), surgical history and current drug use.

The nature of the planned surgery will be documented, as well as the date of the pre-surgical CT scan.

The patient will also be asked to complete two quality of life questionnaires and the CSRI form.

All baseline data will be entered onto the trial electronic database by the site research team.

The randomisation form can also be completed at this point in preparation for randomisation on day of surgery. Note that the form may not be required if the patient is found to be ineligible at point of surgical/fascial closure.

5.4.Day of surgery

The day of surgery may occur on the same day as the baseline visit, and possibly even the day of consent. The patient will undergo surgery as determined by their requirements and as per hospital protocol, but at point of closure, if the patient is considered eligible, they will be randomised to be sutured either by Hughes repair or standard mass closure. The closing surgeon will access the randomisation system to have randomisation group assigned. The skin will be closed as per surgeon's decision.

The C-POSSUM will be completed by the surgeon based on the patient's status prior to surgery. Surgical information will be collected, including grade of operating surgeons and anesthetist, the type and mode of surgery undertaken, duration of the surgery as well as time taken for fascial closure. Details of the fascial closure will also be collected. Surgical complications during will be collected as SAEs.

After the patient has been randomised, the GP letter should be sent. Due to the nature of the study, a significant number of consented patients may not be randomised, and notification to their GP of their involvement in the study prior to randomisation and intervention is not necessary.

5.4.1. Reoperation

If the patient requires a further operation at the site of the colorectal cancer surgical wound prior to discharge, the details of the surgery will be captured, including the closure technique.

An SAE report for the event leading to surgical intervention will need to be completed, and the 30 day SAE collection will restart at point of re-operation.

5.5.Discharge from hospital

The patient will be discharged as per standard hospital care, therefore the day of discharge may vary from patient to patient. At discharge, information will be collected regarding post-operative care, evidence of SSI and any resulting care as well as any incidence of burst abdomen. Any SAEs during the hospital admission will be collected as normal.

Also at discharge, the patient will be provided with a patient diary to complete at home for up to 30 days post-surgery to gather information regarding SSI symptoms. The QoL questionnaires (to be completed at day 30 post surgery) can also be provided to the patient at discharge, so that they can complete at home on day 30. The questionnaires and diary can be returned either by post or in person, depending on site preference.

5.6.Thirty day visit

The 30 day visit can be conducted by phone or in person. At day 30; SAE information will be documented, the patient will stop collecting SSI information in their patient diary, and the QoL questionnaires will be completed. Whether the patient has experienced a burst abdomen post discharge will also be documented at this point.

If the visit is conducted in person, then all documents can be collected during the visit. If the visit is conducted by phone, then the patient should use the stamped addressed envelope provided at discharge to return the questionnaires and diary.

Unreturned questionnaires will be followed-up by resending the questionnaire by post or by a phone call, or both.

If the patient is still in hospital at day 30, the patient diary (SSI) will not require completion. The QoL questionnaires will still require completion even if the patient is in hospital at day 30.

5.7.Six month visit

The 6 month visit can be conducted by phone or in person. At this visit, the patient will complete the QoL questionnaires and CSRI questionnaire.

If it is planned that the visit will occur by phone, the QoL questionnaires and CSRI questionnaires should be sent to the patient by post for completion within the visit window and returned by post. If the visit is to be conducted in person, the questionnaires can be completed on the day of the visit.

Again, unreturned questionnaires will be followed-up by resending the questionnaire or by phone call, or both.

5.8.One year visit

The study team should collaborate with radiology and outpatient department to schedule both the CT scan and clinical examination within the visit window (+/- 2 months). If a patient's treatment course and clinical requirements meant that no CT was undertaken within this window, please select the CT closest to the one year timepoint. The QoL questionnaires and CSRI form can be sent to the patient ahead of the visit to be returned on the day of visit.

5.9.Follow-up visits

The following visits will occur pending further funding. These visits are considered as follow-up for the purposes of the trial, as they follow the primary endpoint visit at one year.

5.9.1. Two year follow-up

The study team should collaborate with radiology and outpatient department to schedule both the CT scan and clinical examination within the visit window (+/- 2 months). If hospital standard practice does not routinely call for a two year CT, or a patient's treatment course and clinical requirements means that no CT was undertaken within this window, please select the CT closest to the two year timepoint. The QoL questionnaires and CSRI form can be sent to the patient ahead of the visit to be returned on the day of visit.

5.9.2. Three, four and five year follow-up

The study team should collaborate with the outpatient department to schedule follow-up appointments for year 3, 4 and 5. The patient will undergo clinical examination for the presence of incisional hernia, and information will be collected on the status of their health. The patient will also be asked to complete the QoL questionnaires and the CSRI form.

Table 3. Patient Schedule

	In advance of surgery	Day 1	(Up to day 30)	Discharge	Day 30[1]	6 month[1]	Year 1[1]	Year 2[1]	Year 3[1]	Year 4[1]	Year 5[1]
		+/- 0			+/- 5 days	+/- 30 days	+/- 2 months	+/- 2 months	+/- 2 months	+/- 2 months	+/- 2 months
Screening[2]	x										
Patient consent	x										
Eligibility[3]	x	x									
Demography	x										
Computed Tomography	X[4]						x	x			
Hernia Clinical Examination	x						x	x	x	x	x
Drug History	x										
Medical History	x										
Surgical History	x										
FACT-C questionnaire	x				x	x	x	x	x	x	x
SF-12 questionnaire	x				x	x	x	x	x	x	x
Randomisation		x									
Abdominal surgery		x									
(Reoperation[5])			(x)								
Wound closure details		x	(x)								
Surgical information		x	(x)								
C-POSSUM		x	(x)								
SSI				x							

	In advance of surgery	Day 1	(Up to day 30)	Discharge	Day 30[1]	6 month[1]	Year 1[1]	Year 2[1]	Year 3[1]	Year 4[1]	Year 5[1]
		+/- 0			+/- 5 days	+/- 30 days	+/- 2 months	+/- 2 months	+/- 2 months	+/- 2 months	+/- 2 months
Patient SSI Diary				x	x[7]						
Cancer staging					x						
Cancer status							x	x	x	x	x
Surgical activity							x	x	x	x	x
Client Service Receipt Inventory (CSRI) questionnaire	x					x	x	x	x	x	x
SAE reporting[6]		x		x	x						
Death				x	x	x	x	x	x	x	x

[1]All visit timings and windows are in relation to date of surgery. [2]Screening can occur at any point up to surgery. [3]Eligibility is established at screening, and requires confirmation at point of randomisation. [4]The diagnostic pre-operative abdominal CT can be taken at any point prior to surgery. If a CT scan does not take place between the time window for the one and two year CT, please select the CT closest to the one and two year timepoint. [5]Reoperation occurs if the wound requires reopening within 30 days of index operation. [6]Information on all SAEs from point of consent to 30 days post intervention will be collected. If the patient requires the abdominal wound to be re-opened during admission, then all SAEs will be collected until 30 days post re-operation. [7]If the patient is still in hospital at day 30, the SSI diary does not need to be completed. Grey text is conditional on further funding and is only applicable to patient recruited into the pilot and main phases of the study.

6. Study Procedures

6.1.Hughes closure technique

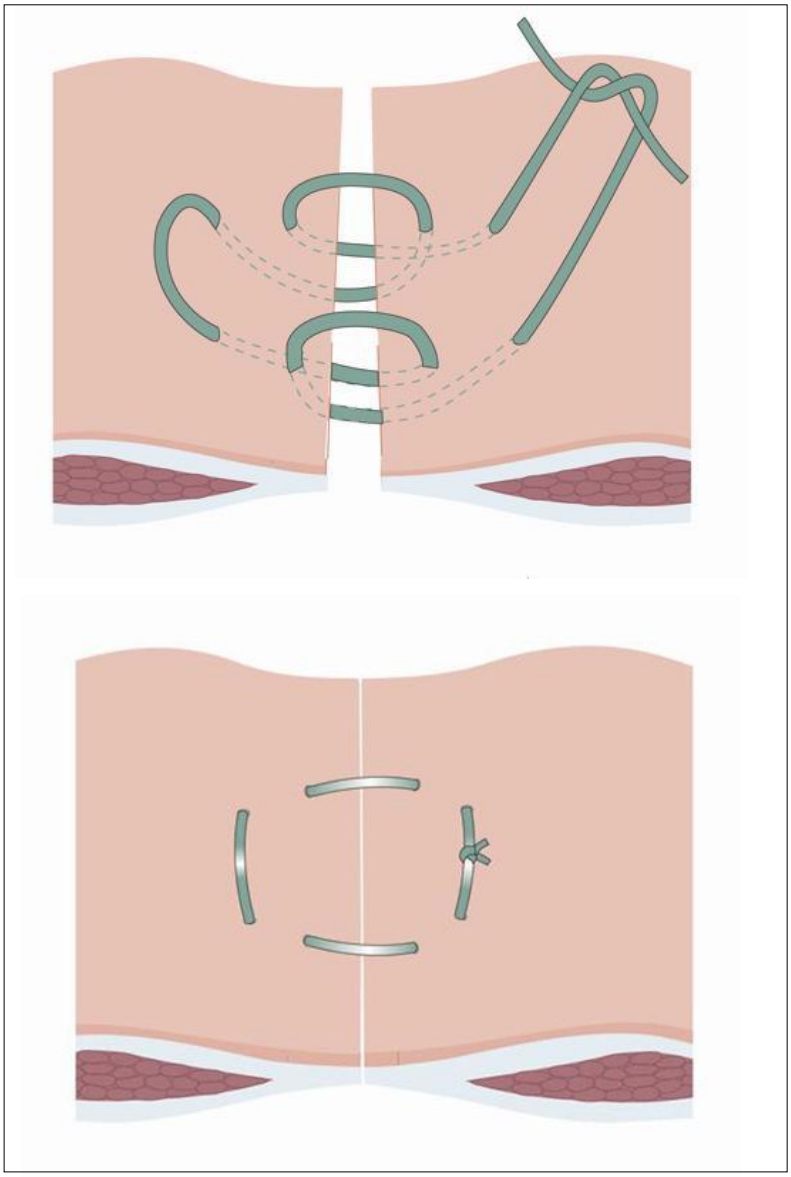

Figure 3. Pictorial of Hughes closure.

Diagram showing the Hughes closure method, using a combination of sutures placed either closer to, or further from, the central incision. When the sutures are pulled to close the defect, the sutures lie both across and along the incision.

The Hughes technique incorporates interrupted double mattress sutures of 1 Nylon to distribute the load vertically along the wound rather than across it. These interrupted sutures are placed, clipped but not tied until a conventional mass closure using two loop 1 PDS sutures from each end of the wound is performed. As the continuous PDS sutures are placed the interrupted Nylon sutures are tied in turn. It is critical that the Nylon sutures are tied "snuggly" rather than tightly to avoid tension and tissue strangulation. At least 5 throws should be placed and the sutures cut close to the knot to minimise the potential risk of suture

granuloma. The interrupted sutures are placed in the following manner (See Figure 3)

i) Far - approximately 1.5cm from edge of rectus sheath
ii) Near – approximately 0.5cm from edge of rectus sheath
iii) Near
iv) Far
v) The suture is then placed on the same side of the wound approximately1.5cm along in the Far position
vi) Near
vii) Near
viii) Far – as a consequence the last suture should end on the same side as the first bite, 1.5cm along and the two ends clipped.
ix) The next suture can be commenced approximately 2cm along from the first.

6.1.1. Training in Hughes closure technique

To assure standardisation of the closure technique, all surgeons participating in the trial will complete training on the Hughes repair and will be assessed by the Chief Investigator (or a designated assessor) and approved only when closure technique is satisfactory.

A reference instructional video will also be provided as well as ongoing quality review of the technique throughout the course of the trial.

6.1.2. Mass closure technique

For the purposes of the study mass closure will be taken to be the responsible consultant surgeon's standard closure technique.

6.2.Clinical Evaluation of incisional hernia, primary endpoint measure

Clinical assessors will be blinded to the closure technique by one of two methods depending on site acceptability and preference. The preferred method would mean the surgical staff *not* documenting in operative notes the exact method of closure but recording a statement similar to 'this patient was included in the HART trial and closed according to randomisation'. The second back-up method will instruct the clinical assessor to complete the hernia examination before reviewing the patient notes.

Clinical examination for incisional hernias will take place at the one year visit, and again at 2, 3, 4, and 5 year follow-ups pending further funding.

Clinical examinations will be conducted by surgeons or colorectal cancer nurse specialists,

who are trained to perform this examination. The examiner will assess the patient ensuring to include the following:

a. With the patient in a standing position, palpate the length of the closed wound and ask the patient to cough or perform the Valsalva manoeuvre
b. With the patient in a supine position, palpate the length of the closed wound and ask the patient to cough or perform the Valsalva manoeuvre

6.3.Radiological Evaluation of incisional hernia, tertiary endpoint measure

NHS radiologists will determine whether there is a hernia present, define it as herniation of the bowel or other intra-abdominal content outside the abdominal wall, identify the presence of other hernias; and the quality of the recti muscle. To optimally measure these criteria, the radiologists will undertake a preliminary review of CT images of patients who have previously received abdominal surgery for colorectal cancer, outside of HART. This will act as an opportunity to standardise measuring techniques and reduce inter-rater variability.

Patients from the feasibility phase of the study will provide paired CT images; pre-surgery and one year post surgery. The analysis of these scans will determine whether the measurements taken can identify changes in incisional hernias over time.

Information gathered from the preliminary review and the feasibility phase of the HART trial will allow the radiologists to amend the measuring techniques if required.

CT images from the pilot and main phase of the study, both pre-operative and post-operative, will be reviewed by the radiologists, who will be blind both to the type of abdominal wall closure and the clinical finding of an incisional hernia.

6.3.1. CT imaging

Scans should be acquired using the thinnest slice thickness capability of the scanner (eg for GE scanner, scans are acquired at 0.625mm slice thickness) and images for review reconstructed to 5mm or 2.5mm slice thickness in axial plane.

Scans should be done using the standard departmental protocol for staging and follow-up scans.

For example, a standard portal renal abdomen and pelvic CT with oral contrast Omnipaque 350 (20mls in 500mls in water), 250mls at 1 hour and 250mls 30 minutes prior to investigation and 10-50mls top up at 0 minutes, and IV contrast with 100mls Niopam 300 3mls/sec

followed by 20mls saline – portal venous phase 70 sec.

6.3.2. Transfer of CT images

The transfer of CT images from participating site to reviewing radiologists will be done using the Picture Archiving and Communications System (PACS) or equivalent.

Relevant images will be requested of the study team at site on a regular basis, most likely quarterly, but dependent on volume of work. Image requests will be made using patient identifiers, but when the image is transferred within PACS, the patient name will remain with the scan. This is a feature of the system, and patient names will only be available to the submitting site and reviewing radiologist at point of review. This information will not be captured elsewhere. The radiologist will be provided with an equivalent list of patient identifiers as the site to allow for identification of the relevant scans on PACS.

7. Safety

The clinical trial safety processes will be conducted according to relevant standard operating procedures.

7.1.Urgent safety measures

The Chief Investigator and Principal Investigators (PIs) may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation from the REC or sponsor. However they must alert the sponsor as soon as possible of any such urgent measures by contacting the Cardiff and Vale UHB R&D Office and CI. The Chief Investigator (CI) or sponsor will notify the Wales RES of the presenting issue within 3 days of the urgent measure setting out the reasons for the urgent measure and the plan for further action. If a site PI identifies the presenting issue, he or she should also inform their local R&D department.

7.2.Adverse events

7.2.1. Definitions

Adverse Event (AE): Any untoward medical occurrence in a clinical trial participant to whom a study intervention has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease.

Serious Adverse Event (SAE): Adverse events are classified as either serious or non–serious. A serious adverse event (SAE) is an adverse event which results in any of the

following:

- Results in death;
- Is life-threatening, in the sense that the patient was at risk of death at the time of the event (but not if the event could have caused death if more severe);
- Requires hospitalisation (or prolongation of existing hospitalisation) defined as an unplanned admission of any length, even if precautionary for continued observation; however pre-planned hospitalisation (e.g. for an elective procedure or a pre-existing condition which has not worsened does not constitute an adverse event);
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect; or
- Is otherwise considered medically significant by the investigator.

Relatedness: Whether the reporting investigator considers the adverse event to be related can be classed as follows:

- Definite
- Probable
- Possible
- Unlikely
- Not related.

Serious Adverse Reaction (SAR): A serious adverse event that is considered related to the procedure.

Expectedness: An AE is deemed expected if listed in section 7.4. AEs not listed will be unexpected.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A serious adverse event that is considered related to the procedure, and unexpected against a predetermined list of events.

7.3. Clavien-Dindo classification

Each SAE will be assessed according to the Clavien-Dindo classification of surgical complications [41].

7.4.List of expected adverse events

Below are listed AEs that are considered expected for patients undergoing colorectal surgery. However, if the following events lead to death, that would be considered

unexpected. These events may be classified as serious and will be recorded as such but will not require reporting to REC:

- Lower Respiratory Tract infection
- Urinary Tract infection
- Anastomotic Leak
- Intra-abdominal sepsis
- Deep vein thrombosis
- Pulmonary embolus
- Wound infection
- Surgical site infection
- Wound breakdown
- Paralytic ileus
- Bleeding
- Myocardial infarction
- Stoma complications; prolapsed, retraction, dehiscence or hernia.

7.5. Adverse events of special interest

Additional information may be requested for adverse events of special interest.

- Wound breakdown
- Surgical site infections

7.6. Adverse event recording and reporting

Information on all SAEs from point of consent to 30 days post intervention will be collected. If the patient requires the abdominal wound to be re-opened up to 30 days after the index operation, then all SAEs will be collected until 30 days post re-operation. All deaths, regardless of timing is to be reported as an SAE. The PI or delegate will review all SAEs collected at their site; they will assign relationship to closure technique as described in section 7.2.1 and expectedness against the list provided in section 7.4.

All SAEs are to be reported to the CTU within 24 hours of knowledge via the electronic database. Paper SAE forms are available for data collection in the first instance. All reported SAEs will be monitored by the central study team and data clarifications requested if required.

If the electronic database is unavailable due to technical issues for an extended period, the central study team will implement a paper based reporting system to the safety email address which will be provided if required.

The central study team will provide safety updates quarterly to the study sites, and as outlined in relevant processes to other interested bodies.

Confirmed SUSARs will be reported to REC and sponsor within 15 days of knowledge by the central study team. At the same time, the relevant site study team will be informed who will in turn inform their R&D department if required as a condition of the study approval.

8. Randomisation and analysis

8.1.Randomisation

An adaptive randomisation design will be used to allocate eligible patients to groups of similar size [42]. Randomisation will be done by the closing surgeon and will take place during surgery and as close as possible to the time when the surgeon commences closure.

8.2.Sample size estimation

Our opportunistic retrospective clinical review suggested that the difference in IH rates between the Hughes Repair and mass closure could be as high as 18%. Based on data from that and our systematic literature review, we seek to identify a more modest, but still clinically important, reduction in IH rates from 30% for mass closure to 20% for the Hughes Repair. To give 80% power of detecting this difference with a 5% significance level requires us to follow up 640 patients at one year. As loss to follow up from similar trials (e.g. COGNATE [43]) is about 20% at one year, we aim to recruit 800 patients in total. This target is similar to, but slightly greater than, those of recent trials comparing different closure techniques for reducing IHs (737 [44], 600[45] and 576 [26]). A completed sample of 640 participants will also yield 80% power of detecting with a 5% significance level with a standardised difference of 0.225 in QoL (the principal second outcome). Thus HART, powered to detect an important difference of 10% in the binary clinical outcome of IHs, will also detect a difference generally regarded as small in the more patient-centred quantitative outcome of QoL.

8.3.Analysis

Analysis will be undertaken as outlined in the Statistical Analysis Plan (SAP). The Trial Steering Committee and an independent Data Monitoring Committee (DMC) will be asked to review and comment on the SAP prior to any analysis of the data. A single main analysis will be performed at the end of the trial when all one year visits have been completed. Consideration of the frequency of monitoring visits and any criteria for stopping rules will be discussed and agreed with the DMC prior to recruitment starting. The SAP and DMC charter will document the agreed timings and strategy.

9. Publication, authorship and dissemination

The findings of the trial will be presented at departmental, regional and national surgical meetings. There are plans to publish the results in peer-reviewed journals and thus to disseminate them through the clinical scientific community. Service users will be able to access the study results through local staff undertaking the study and their general practitioners as the results are published. Papers will be published by the lead applicants on behalf of the HART collaborative which will include all principal investigators and their nominated co- investigators where their unit recruits more than 5 patients.

10. Ethical considerations and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013) and the principles of Good Clinical Practice and in accordance with all applicable regulatory guidance, including but not limited to the Research Governance Framework for Health and Social Care in Wales (2nd ed, 2009) or applicable frameworks in the other UK countries.

This protocol and related documents (and any subsequent amendments) will be submitted for review to Research Ethics Committee Wales 3. Annual progress and safety reports and a final report at the conclusion of the trial will be submitted to the REC within the timelines defined.

CT scans at year 1 and 2 are required as part of standard care, but IRMER assessment is required to be undertaken. Since no radiotherapy treatment is provided as part of this study protocol ARSAC approval is not required.

The study will respect the rights of participating patients and ensure confidentiality of patient information. Patients undergoing surgery for colorectal cancer have an excellent support system through the specialist cancer nurses and the clinical team, as well as several charities and voluntary organisations. Should participants have additional questions about the trial, advice will be available from both within the research team and outside of the research team in the form of websites such as the nhs website page: Clinical trials and medical research - Joining a trial, found on http://www.nhs.uk/Conditions/Clinical-trials/Pages/Takingpart.aspx.

10.1. Quality Assurance

The trial will be monitored to ensure that the study is being conducted as per protocol adhering

to Research Governance, and the principles of GCP. The purpose of monitoring will be to ensure that the local site facilities and personnel continue to be fit for purpose. The approach to, and extent of, monitoring (specifying both central and on-site monitoring) will be specified in a trial monitoring plan which is determined by a risk assessment, undertaken prior to start of trial.

10.2. Data Handling and Record Keeping

Clinical data will be entered into the electronic database capture system by delegated investigators or research nurse working at each hospital site.

Results from the analysis of scans will be entered into electronic database capture system by the delegated radiologists.

Staff in the trial office will work closely with the site staff and radiologists to ensure that the data are as complete and accurate as possible. An extensive range and consistency checks will further enhance the quality of the data.

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's personal details (name, address) will be stored by sites under the guidelines of the 1988 Data Protection Act and not entered onto the trial database. Participants will be allocated an individual specific trial number and this alone will be used to identify their data on the HART trial database. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

11.End of trial

The definition of the end of the trial will be the date of the last one year visit for the final patient undergoing the trial. Pending funding, follow-up information will be gathered until 5 years post-surgery. If this is the case, then the end of trial will be the last 5 year visit for the final patient.

Discontinuation of the trial will occur if the trial is felt not to be in the best interest of the patients. Data review by the DMC may lead to a recommendation to halt the study, but the final decision will rest with the sponsor after consideration of recommendations by the chief investigator and TSC.

An end of study declaration form will be submitted to the sponsor, main REC and R&D offices within 90 days from completion of the trial and within 15 days if the trial is discontinued

prematurely.

A summary of the trial report/publication will be submitted to the main REC and sponsor within 1 year of the end of trial.

Within 2 weeks of the end of the contract with the funding body, a final draft report will be submitted which will be developed into a final publication within a year.

11.1. Archiving

The Trial Master File (TMF) containing essential documents will be archived at an approved storage facility for a minimum of 5 years after end of trial. The Principal Investigators at each site are responsible for archiving the Investigator Site File (ISF) and essential documents pertaining to the trial for the same duration. Trial data must not be destroyed without written permission from the Sponsor, who is responsible to ensuring trial data is archived appropriately.

12. Protocol amendment log

			Implemented at
Version 2.5,	20Nov2012	N/A	At feasibility phase
Version 2.7,	01Mar2013	Substantial amendment number 1	At feasibility phase
Version 2.8,	18Apr2014	Substantial amendment number 2	At pilot phase
Version 2.9,	21Nov2014	Substantial amendment number 3	At pilot phase
Version 3.0,	19Mar2015	Substantial amendment number 4	At pilot phase
Version 4.0,	21Oct2015	Substantial amendment number 5	At pilot phase

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