HART
Hughes Abdominal Repair Trial

Statistical Analysis Plan

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Hughes Abdominal Repair Trial. Abdominal wall closure techniques to reduce the incidence of incisional hernias: study protocol for a randomised controlled trial

Short title: Hughes Abdominal Repair Trial (HART).

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Abbreviations and Definitions

AAA	Abdominal aortic aneurysm
ACCEPT	Acceptance Checklist for Clinical Effectiveness Pilot Trials
AE	Adverse Event
BNF	British National Formulary
CEAC	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
COGNATE	Cancer of Oesophagus or Gastricus—New Assessment of Technology of Endosonography
CONTINT	CONTinuous versus INTerrupted abdominal wall closure after emergency midline laparotomy (RCT)
C-POSSUM	Colorectal Physiological & Operative Severity Score for Understanding Mortality and Morbidity
CRC	Colorectal Cancer
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CT	Computerised Tomography
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GP	General Practitioner
HART	Hughes Abdominal Repair Trial
ICER	Incremental Cost-Effectiveness Ratio
IH	Incisional Hernia
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
PROM	Patient-Reported Outcome Measure
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SF12 or SF36	Short Form 12 or Short Form 36
SOPs	Standard Operating Procedures
SSI	Surgical Site Infection
STU	Swansea Trials Unit
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TS	Trial Statistician
TSC	Trial Steering Committee
UHW	University Hospital of Wales
UK	United Kingdom

1. Synopsis of trial protocol

1.1. Introduction

This is the plan for statistical analysis of the HART Trial which is a multi-centre randomised controlled trial (RCT) with an economic component involving 28 sites in the UK (Cornish et al., 2016). The primary aim of this RCT is to compare the incidence of incisional hernias (IH) identified by clinical examination over one year from colorectal cancer surgery between two surgical techniques for abdominal wall closure: namely, Hughes Repair (Hughes and Webster, 2011, Shukla et al., 1998) and 'standard Mass' Closure.

The feasibility phase recruited 30 patients at a single site, the University Hospital of Wales in Cardiff. The pilot phase comprises patients recruited at further selected sites, and the main phase is now recruiting patients from 28 sites in the UK. The target sample size is 800 including the patients from the pilot phase. Patients recruited may receive either elective or emergency surgery; other inclusion and exclusion criteria, and further details on timelines are given in the study protocol (Cornish et al., 2016).

Eligible and consenting patients are randomised to receive either a Hughes Repair or Standard Mass Closure. The randomisation algorithm uses a dynamic allocation method (Russell et al., 2011) to assign patients to groups of similar size. The randomisation is done as close as possible to the time prior to when the surgeon commences closure (Cornish et al., 2016).

The primary outcome measure is the incidence of incisional hernias (IH) over one year since surgery, as determined by clinical examination of the abdomen by surgeons or trained specialists. Patients are also assessed using radiological imaging through computerised tomography (CT). Two Patient Reported Outcome Measures (PROMs) - namely, the generic Quality of Life (QoL) SF-12 (www.sf-36.org) and the condition-specific Functional Analysis of Cancer Therapy – Colorectal (FACT-C) (Ward et al., 1999) are used to collect at baseline, 30 days, 6 months and 1 year in order to assess the differences between the two study arms. Information regarding post-operative care, evidence of surgical site infections (SSI) and any resulting care as well as any incidence of burst abdomen are collected at discharge. Any SAEs during the hospital admission and up to 30 days post-surgery are collected as normal.

Case Report Forms (CRFs) are used to collect data on conditions associated with an increased risk of developing hernias (e.g., diabetes and obesity) and for calculating a Colorectal – Physiological and Operative Severity Score for Understanding Mortality and Morbidity (C-POSSUM) score (Shukla et al., 1998). CSRI (Client Service Receipt Inventory) provides data on use of health care resource associated with the two procedures.

Data analysis will also: assess risk of mortality and morbidity in patients undergoing colorectal surgery; estimate the effect of various factors on IH rates; investigate whether some patient groups derive greater benefit from either of the two surgical techniques; and compare the

cost-effectiveness of the two procedures. The study is currently funded for 1 year which covers the primary and secondary objectives, the tertiary objectives will be analysed provided that further funding is available.

1.2. **Objectives**

Primary objective:

1) To compare the incidence of incisional hernias over one year from colorectal cancer surgery between the Hughes and standard mass closure.

Secondary objectives:

2a) To compare quality of life over one year following colorectal cancer surgery between the Hughes and standard mass closure (the principal secondary aim).

2b) To evaluate the cost-effectiveness of the Hughes Repair relative to standard Mass Closure over the first year.

2c) 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.

2d) To identify and characterise patient and surgical factors which increase the risk of developing incisional hernias.

2e) To estimate prevalence of incisional hernias at one year following surgery for colorectal cancer in patients receiving Hughes or standard mass closure.

2f) To compare the quality of life between patients with incisional hernias and those without incisional hernias over one year.

Tertiary objectives:

3a) To assess the prevalence of clinically detectable incisional hernias at five years from surgery.

3b) To evaluate the effect of the Hughes Repair on participants' quality of life over five years from surgery.

3c) 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.

3d) 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.

3e) 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. Study Methods

2.1. Trial design

This is a multicentre, RCT where patients will be randomised as 1:1 to compare two suture techniques for the closure of the midline abdominal wound following surgery for colorectal cancer.

2.2. Interim analysis and stopping guidance

There will be no interim analysis. However, there will be the possibility of stopping the study early should there be a safety concern. Responsibility for stopping early (if required) will sit with the sponsor and DMC, and 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. The TSC additionally will monitor recruitment and study progress to inform a decision to halt the study should it be considered that they study will fail to deliver its objective due to delayed recruitment or lack of data.

2.3. Final analysis

A single main analysis will be performed at study end, when all 1 year visits have been completed, data collated and locked. Statistical analysis will commence after the Statistical Analysis Plan (SAP) has been finalised (signed off by CI and Trial Statistician) and the study data locked. The statistician will receive unblinded data after the database is locked for the final data analysis and report. All outcomes will be analysed collectively at the end of the trial and completed within the timeframe agreed by the study team.

2.4. Further analysis (pending funding)

Pending further funding, a further analysis will take place at 5 years, when all visits have been completed, data collated and locked.

3. 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 eligible for inclusion.

3.1. Setting

The study is being performed in general surgical units within the NHS and currently recruiting patients from 28 sites across the United Kingdom. This study has ethical approval from Wales REC 3 (REC 12/WA/0374).

3.2. 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 5 cm or more

3.3. **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 abdominoperineal wound closure

3.4. **Randomisation and blinding**

An adaptive randomisation design has been used to allocate eligible patients to groups of similar size. The closing surgeon perform this telephone randomisation during the surgery and as close as possible to the time of commencing the closure. The trial statistician is blinded until the data has been locked for the main analysis.

3.5. **Analysis populations**

The primary analysis will include all patients as originally allocated after randomisation (defined as Intention to treat population) which reflects the pragmatic nature of the trial design.

4. Statistical Principle

4.1. **Sample Size and Statistical Power**

The clinically important difference in the study arms was assumed to have a reduction in IH rates from 30% for the Mass Closure group to 20% in the Hughes Repair group. To detect this difference, a total of 640 patients will be required providing 80% statistical power with 5% level of significance. As loss to follow up from similar trials (such as the COGNATE trial (Russell et al., 2010)) is about 20% at one year, HART therefore aims to recruit a total of 800 patients.

A completed sample of 640 participants will also yield 80% power of detecting (with a 5% significance level) a standardised difference of 0.225 in QoL (the principal second outcome). Thus, HART, powered to detect an important difference of 10% in the primary binary clinical outcome of IHs, will also have the power to detect a difference generally regarded as small in the more patient-centred quantitative outcome of QoL.

4.2. Links between Objectives & Outcomes

Objective	Measure
Primary Objective	
Objective 1: To compare the incidence of incisional hernias over one year from colorectal cancer surgery between the Hughes and standard mass closure.	This comparison will be based on the number of incisional hernias (events) over one year and total number of years of follow-up (person-years) in each treatment group (Hughes Repair and Mass Closure) as assessed by the clinical examination of the abdomen.
Secondary objectives:	
Objective 2a: To compare quality of life over one year following colorectal cancer surgery between the Hughes and standard mass closure.	For this comparison two Quality of Life PROMS (SF-12, FACT-C) at baseline, 30 days, 6 months and 1 year will be used to assess the difference between the patients with Hughes Repair or Mass Closure.
Objective 2b: To evaluate the cost-effectiveness of the Hughes Repair relative to standard Mass Closure over the first year.	Surgery and subsequent healthcare resource (in year one) will be collected on CRFs and CSRI, respectively and unit costs will be applied using published sources or hospital financial and purchasing information. These costs will then be compared to health and QoL outcomes by calculating ICERs.
Objective 2c: To test whether the Hughes Repair reduces the risk of postoperative 'burst abdomen' (complete abdominal wound dehiscence) between the Hughes and standard mass closure by day 30.	Data on the incidence of post-operative 'burst abdomen' or full thickness abdominal wall dehiscence will be collected.
Objective 2d: To identify and characterise patient and surgical factors which increase the risk of developing incisional hernias.	Data will be collected regarding patient demographics and conditions that are considered to be associated with an increased risk of developing hernias, including but not limited to diabetes and obesity, C-POSSUM and the presence of other hernias (incisional and non-incisional). All these could contribute as risk factor(s).
Objective 2e: To estimate prevalence of incisional hernias at one year following surgery for colorectal cancer in patients	The point prevalence of IH by arms will be calculated at one year following the surgery. To estimate the prevalence, use the number of IH cases and the total number of patients for each of the arms will be used.

Objective	Measure
receiving Hughes or standard mass closure.	
Objective 2f: To compare the quality of life between patients with incisional hernias and those without incisional hernias over one year.	The quality of life of patients with or without incisional hernias will be compared over one year using PROMs (SF-12 and FACT-C) collected at baseline, 30 days, 6 months and 1 year.
Tertiary objectives:	
Objective 3a: To assess the prevalence of clinically detectable incisional hernias at five years from surgery.	The prevalence of incisional hernias at five years as measured by clinical examination will be assessed. This will be calculated by using the total number of IH cases and total number of patients at five years.
Objective 3b: To evaluate the effect of the Hughes Repair on participant's quality of life over five years from surgery.	During the annual review, both SF-12 and FACT-C QoL questionnaires will continue to be completed to assess the QoL over 5 years.
Objective 3c: 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.	CRFs and CSRI will be used to collect information on surgery and subsequent resource use over 5 years. The unit costs will be applied using published sources or hospital financial and purchasing information. These costs will then be compared to health and QoL outcomes by calculating ICERs.
Objective 3d: 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.	We will calculate sensitivity and specificity of CT image to identify IHs by considering the Clinical examination as the gold standard. This comparison will be done between two periods of data: first 2 years of CT scans will be compared with the 2-5 years clinical examination data.
Objective 3e: To compare the quality of life between patients with incisional hernias and those without incisional hernias in both arms over five years.	Likewise the objective 2f, the quality of life of patients with or without incisional hernias will be compared over 5 years using PROMS (i.e. SF-12 and FACT-C).

4.3. **Protocol deviations**

A protocol deviation occurs when the activities during a study diverge from the approved protocol; a variance from protocol. Protocol deviations will include the following, but may include others:

- Visits outside of permitted time windows
- Questionnaires completed outside of permitted time windows
- Missing questionnaires
- Trial activities prior to consent
- Patient closed not according to randomisation

4.4. **Protocol violations**

A protocol violation occurs when there is a divergence from the approved protocol (a deviation) that also:
-reduces the quality or completeness of the data
-impacts a subject' safety, right or welfare
-affects the scientific integrity
Protocol violations will include the following, but may include others:

- Lack of valid consent

5. Analysis strategy

5.1. **Statistical and Health Economic Analysis**

The main statistical analysis will address all the study objectives except those related to the cost-effectiveness of the interventions (objectives 2b and 3c). Statistical hypotheses will be assessed using a 5% significance level. The baseline comparability of the randomised groups will be presented by reporting summary statistics. Table of summary statistics will be produced including but not restricted to the age, sex, ethnicity, BMI, medical history, surgical history, and QoL measures (FACT-C, SF12). Continuous variables will be summarised using the following statistics; n (non-missing sample size), mean, standard deviation, median, minimum, and maximum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. The number of missing cases will be reported by arms. Data to be presented as in **Table 1**.

Objective 1 (Comparison of IH incidence rates)
To address the objective 1, IH incidence rate will be calculated by the number of incisional hernias (events) over one year and person-years of follow-ups for both groups of patients having the Hughes and the 'standard mass' closure. Poisson regression model adjusting by (but not limited to) age, sex, BMI, diabetes, smoking status, history of IH, AAA and COPD (see **Table 2** and **Table 3**) will be used to compare these rates by study arms. The over-dispersion nature of the data will be explored by checking the distribution of the count data. In such cases, an appropriate model (e.g. Zero-inflated Poisson regression, Negative Binomial regression model) will be used as required.

Objective 2a (Quality of Life at baseline, 30 days, 6 months and 1 year)
PROMs (SF-12 and FACT-C) will be used to measure the quality of life of patients over one year (collected at baseline, 30 days, 6 months and 1 year) using summary statistics to measure the QoL at all these time points. To compare these QoL measures between the two arms (Hughes and standard) mixed model and repeated measures will be used adjusting for baseline QoL (i.e. SF12, FACT-C), important demographic and clinical prognostic factors (e.g., POSSUM score, sex, BMI, diabetes, history of IHs, AAA, SSI, reoperation, and stoma). The corresponding dummy tables are presented in

Table 4 and **Table 5**.

Objective 2b (Cost effectiveness of Hughes vs Standard Mass)

The health economic evaluation will compare the cost-effectiveness of Hughes Repair relative to Mass Closure. This will be done from an NHS perspective using cost-effectiveness and cost-utility analyses. Discounting of 3.5% of both costs and benefits will be applied where data collection exceeds 1 year post randomisation.

In order to establish the costs for Hughes Repair and Mass Closure, resource use will be collected in 3 categories: 1) surgery, 2) complications/adverse events and 3) other healthcare usage.

1) Potential differences in surgical procedures will be collected using the information provided on the intra-operative CRF including mode of operation, suture details and level of postoperative care with the key parameters influencing cost of surgery expected to be grade of surgeon and time of procedure. Data on reoperations will be obtained from the reoperation CRF. In addition to the cost of surgery, the cost of the initial hospital stay will be calculated using length of stay data based on hospital admission and discharge dates.
2) Data of post-operative complications (i.e. surgical site infection, burst abdomen, other complications and management) and other adverse events will be obtained from the discharge CRF and SSI diaries.
3) Number of other healthcare contacts (GP, nurse, new hospital admission excluding the initial hospital stay for operation etc.) will be established using patient diaries at 30 day follow-up and a CSRI (based on (Beecham J.) adapted by STU specifically for healthcare resource use collection in colorectal surgery) at 6 months and 1 year follow up. This will be compared to other healthcare resource use collected using the CSRI at baseline and adjusted for differences in trial arms if required. The one year follow-up will provide information on the number of repeat operations and readmissions, additional abdominal operations and stitch sinuses as well as length of stay of readmissions. Costs will then be allocated using published sources (Personal Social Services Research Unit, NHS reference costs, BNF) and information from hospital purchasing and finance departments. By adding up the costs of surgery, adverse events (including SSI, burst abdomen and reoperation) and subsequent other healthcare for all patients we will be able to compare the total and mean costs (per patient) of the two treatments and calculate incremental costs (or cost savings) of the intervention. These incremental costs will then be used to undertake the following analyses:

a) For the primary economic analysis, the costs will be compared to the primary outcome (number of incisional hernias) at 1 year follow up in a cost-effectiveness analysis which will calculate the incremental cost-effectiveness ratio (ICER) for Hughes Repair reported as cost per incisional hernia avoided.
b) A cost-consequence analysis will present costs compared to other outcomes in a tabular form (see **Table 6**).

c) The cost-utility analysis will use SF-6D scores (derived from SF-12 questionnaires) to calculate ICERs as cost per quality adjusted life year (QALY) (Kharroubi et al., 2007). If one treatment is dominant (lower cost, greater effect) then that treatment is unambiguously more cost-effective. In the case of non-dominance, results will be reported as an ICER which shows the extra cost of producing one extra QALY. In order to decide whether the treatment which is clinically more effective offers good value for money, the ICER will be assessed against the monetary thresholds representing the maximum the NHS is prepared to pay for an extra QALY (currently £20,000 to £30,000).

d) Sensitivity analysis will be undertaken as, due to imperfect information on the effectiveness of the interventions and on the resources consumed for treatment, both costs and effects of medical interventions are likely to be associated with some degree of uncertainty. Deterministic one-way sensitivity analysis will therefore recalculate ICERs using reasonable changes in key parameters (usually the 95% CI) to estimate the effect of uncertainty surrounding the estimates of costs and effects. Additionally, probabilistic sensitivity analysis will enable quantification of the uncertainty surrounding the estimates of all costs and effects. Results will be expressed as percentage probability of the intervention being cost-effective at the accepted willingness to pay threshold. Furthermore, cost-effectiveness acceptability curves (CEACs) will be used to demonstrate the probability of Hughes repair to be cost-effective at a range of willingness to pay thresholds.

All analyses will take into account baseline values and adjust for differences in groups at baseline prior to analysis. Missing baseline data will be addressed using mean imputation. Other missing data will be dealt with as outlined in section 5.2.

Objective 2c (incidence of post-operative burst abdomen)

Few cases of post-operative 'burst abdomen' by 30 days after surgery are anticipated in either arm. The proportion of this event will be calculated by arms using statistical test of hypothesis (i.e. Z-test) with confidence interval for any significance difference (**Table 7**).

Objective 2d (patient and surgical factors that increase risk of IH)

A binary logistic regression model will be adopted to identify prognostic factors influencing the risk of developing IH; potential prognostic factors include: patient age and gender, comorbidities (such as indicators for diabetes, cardiovascular conditions, the presence of other hernias and post-operative SSIs), obesity, and C-POSSUM scores, A Cox Proportional Hazard model will be used to assess whether there is a statistical significant difference in the time of developing the IH between the two treatment groups and these related factors or covariates (e.g. age, sex, ethnicity, previous / current medical history (Diabetics, COPD, Hepatic failure), abdominal surgery history, suture size, presence of IH influencing the development of the IH with time. Please see

Table 8 and **Table 9**.

Objective 2e (prevalence of IHs)

The prevalence of IH will be calculated at one year following the surgery for each arm by the proportion of 'the number of IH cases at one year' and 'the total number of patients' for each of the arms. We will assess the prevalence of clinically detectable incisional hernias at five years from surgery. **Table 10** will be used to present the results.

Objective 2f (Quality of Life over 1 year)

PROMs (SF-12 and FACT-C) will be used to measure the quality of life of patients over one year (collected at baseline, 30 days, 6 months and 1 year). Summary statistics will be used to measure the QoL at all these time points. At each of these time points, the comparison between with and without the incisional hernias (IH) will be made. The **Table 11** will be used to present the results.

Objective 3a (Prevalence of hernia over 2-5 years)

The prevalence of IH at 2, 3, 4 and 5 years following the surgery for each arm by the proportion of 'the number of IH cases at year 2, 3, 4 and 5' and 'the total number of patients' for each of the arms. **Table 12** will be used to present the results.

Objective 3b (Quality of life over 2-5 years)

PROMs (SF-12 and FACT-C) will be used to measure the quality of life of patients over 2-5 years using summary statistics to measure the QoL at all these time points. To compare these QoL measures between the two arms (Hughes and standard) mixed model and repeated measures adjusting for baseline QoL (i.e. SF12, FACT-C), important demographic and clinical prognostic factors (e.g., POSSUM score, sex, BMI, diabetes, history of IHs, AAA, SSI, reoperation, and stoma). **Table 13** and **Table 14** will be used to present the results.

Objective 3c (Cost effectiveness of Hughes vs Standard Mass over 2-5 years)

Refer to Objective 2b; analyses a to d will be repeated at 5 years follow up using 2-5 years follow up outcomes and resource use data providing (see **Table 6**).

Objective 3d (Sensitivity and specificity of CT image)

CT images of the study (both pre-operative and post-operative) will be reviewed by the radiologists. They are blinded both to the type of abdominal wall closure and the clinical finding of an incisional hernia. The true positive (sensitivity), false positive, true negative (specificity) and false negative values of detecting incisional hernia by using CT image will be calculated with respect to clinical diagnosis. Thus 'CT Scan' is the index diagnostic test and 'Clinical Examination' is the reference (gold) standard. The Receiver Operating Characteristics (ROC) curve will be calculated which will provide the area under the curve and detect the best combination of Sensitivity and Specificity of CT image identification of hernias over 2 years

compared with clinical examination data over 2-5 years following the surgery. The resulted table will be similar to **Table 15** and **Table 16**.

Objective 3e (Quality of life 2-5 years)

Refer to objective 2f; we will perform similar analysis for 2-5 years to summarise and compare the QoL measures between the groups with and without IHs. **Table 17** and **Table 18** will be used to present the results.

5.2. **Handling of missing data**

Every effort will be made by the study team to capture full data. In case of any missing data, three methods will be used to impute the missing data points: worst case imputation, last observation carried forward and, mean value of the non-missing cases. If needed sensitivity analysis will be carried out with the three imputed data sets and the complete case data set. A consistent approach will be adopted to missing data relating to both effectiveness and cost-effectiveness except where individual outcome measures require some variation in that approach. Participants without follow-up data will be excluded and the frequency of missing data (directly influencing the sample size in some analyses) will be summarised for each variable. If there is reason to suspect that data are not Missing Completely At Random (MCAR), the trial statistician and chief investigator will discuss the findings. Appropriate imputation method will be used if there is no reason to suspect that data are not MCAR (Briggs et al., 2003).

5.3. **Summary of safety data**

All enrolled patients will be included in the safety analysis. The principles of GCP will be followed for this surgical trial. There are a number of SAEs that are expected for patients undergoing colorectal surgery and radiotherapy (please see the protocol for the list of SAEs and adverse events). All SAEs within 30 days of surgery and all deaths (regardless of time after report) are reported by the site staff and reviewed on weekly basis by the CI. Events reportable to the Ethics Committee are identified during the weekly review and submitted to the committee by the CI and trial manager (or delegate). A six-monthly report is also provided to the research ethics committee. The sponsor will receive the same safety information. The SAEs will be summarised by the numbers and patients by arms. Death, life threatening and other seriousness criteria will be listed by arms along with the number of respective patients. For each arm, SAEs types (e.g. Respiratory disorders, Gastrointestinal disorders) will be reported by the number of SAEs, number of patients involved and number of life threatening. The grading of SAEs by arms will be provided using the Clavien-Dindo classification. **Tables 19-24** will be used to summarise the safety data. Similar tables will be used over one year and 2-5 years' time points.

6. Presentation of Data for Analysis

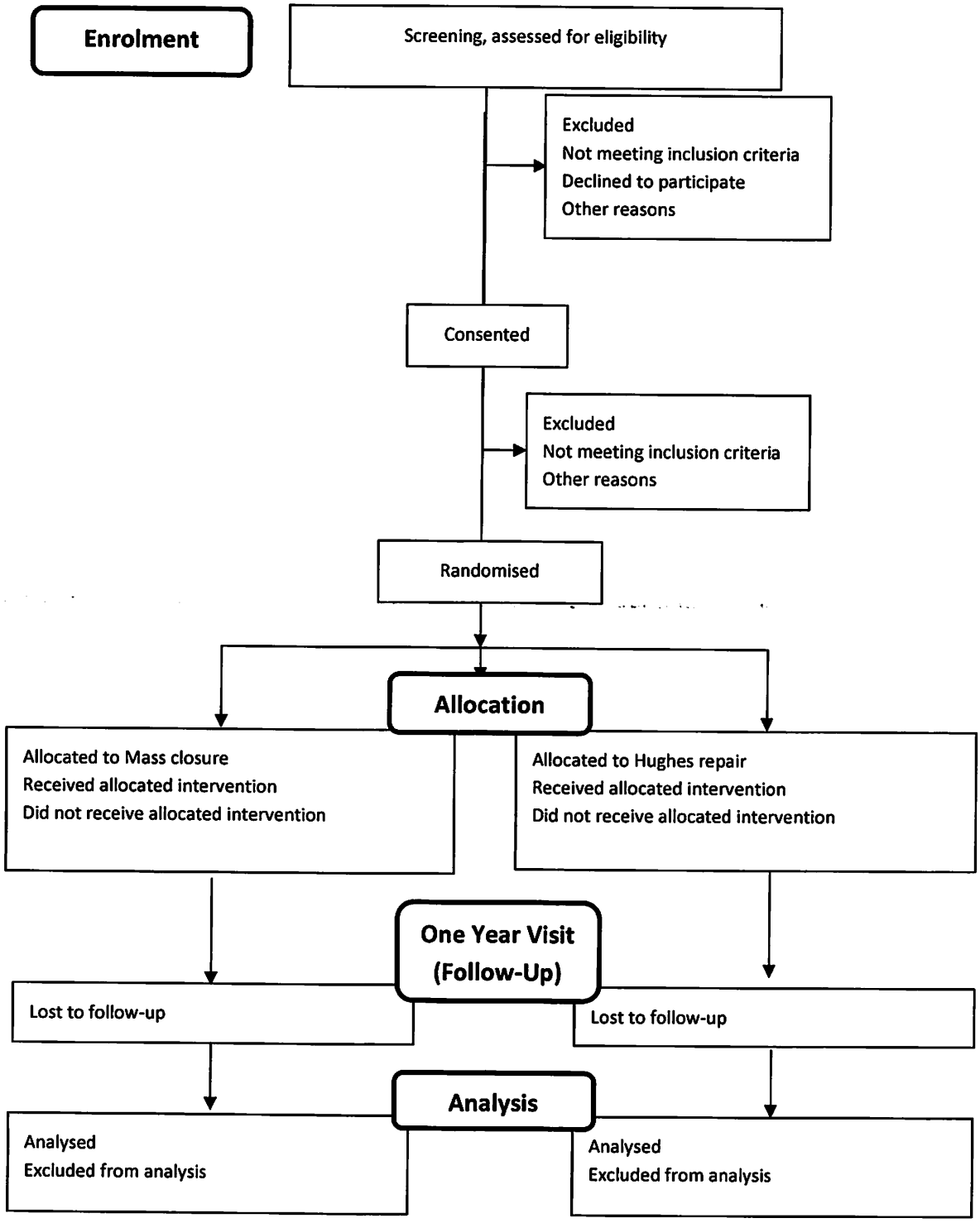
- The Data manager working in conjunction with the Trial manager and in consultation with the trial statistician if required should ensure all data presented to the trial statistician are clean and validated.
- The study database should be locked (as per STU SOPS) by the data manager or the person responsible for the data prior to any analysis undertaken by the trial statistician.
- Once the database is locked, no further amendments will be made unless absolutely essential due to identification of inaccurate data. Any amendments should be requested in writing with full explanation, and changes fully documented.

7. Statistical Software

Analysis will be carried out using SPSS.

8. Appendices

8.1. Appendix 1: CONSORT diagram



8.2. Appendix 2: Dummy Tables

Table 1: Summary of baseline characteristics

	Hughes repair	Standard Mass Closure	Total
Age (years) Range	n, m, sd, med, min, max, [nmiss]	n, m, sd, med, min, max, [nmiss]	n, m, sd, med, min, max, [nmiss]
Female (%)	n (%)	n (%)	n (%)
Ethnicity Caucasian Black Asian Others	n (%)	n (%)	n (%)
Body mass index	n, m, sd, med, min, max, [nmiss]	n, m, sd, med, min, max, [nmiss]	n, m, sd, med, min, max, [nmiss]
Diabetics mellitus	n (%)	n (%)	n (%)
Chemotheraphy* Yes No	n (%)	n (%)	n (%)
Radiotheraphy* Yes No	n (%)	n (%)	n (%)
COPD† Yes No	n (%)	n (%)	n (%)
AAA†† Yes No	n (%)	n (%)	n (%)
Smoking Yes No Ex-smoker	n (%)	n (%)	n (%)
High alcohol use Yes No	n (%)	n (%)	n (%)
ASA grade 1 2 ≥3	n (%)	n (%)	n (%)
QoL SF12 FACT-C	n, m, sd, med, min, max, [nmiss]	n, m, sd, med, min, max, [nmiss]	n, m, sd, med, min, max, [nmiss]
Abdominal Surgery History Yes	n (%)	n (%)	n (%)

No			
Current Hernia Status Yes No	n (%)	n (%)	n (%)

*n = non-missing sample size, m = mean, sd = standard deviation, med = median, min = minimum, max = maximum, nmiss = number missing covariate information; * = Neoadjuvant for colorectal cancer; † = chronic obstructive pulmonary disease; ††= Abdominal aortic aneurysm*

Table 2: Incidence of incisional hernias (IH) at one year (primary end point)

	Hughes Method	Standard Method	p-value
Incisional Hernias	n (%)	n (%)	
Incidence rate of IH	n (%)	n (%)	

Table 3: Parameter estimates of Poisson regression model of IH at one year

Parameters	Coefficient (B)	Exp(B)	95% CI for Exp (B)	p-value
Intercept				
Arms (Hughes, Standard)				
Age				
Sex (male)				
BMI				
Diabetes				
Smoking Status				
History of IH				
AAA				
COPD				

Dependent Variable: Number of IHs

Table 4: Summary of QoL at time points of from baseline to 1 year.

QoL measures	Time points	Hughes Method (n, Mean score)	Standard Method (n, Mean score)	p-value	t-test statistic (Pr(>|t|))
SF12	Baseline				
	30 days				
	6 months				
	1 year				
FACT-C	Baseline				
	30 days				
	6 months				
	1 year				

Table 5: Mean changes and effect sizes of QoL measures (baseline to 1 year)

QoL measures	Time points	Hughes Method			Standard Method			Difference		
		n	Mean Change	ES *	n	Mean Change	ES *	Difference	95% CI	ES*
SF -12 score†	Baseline									
	30 days									
	6 months									
	1 year									
FACT - C†	Baseline									
	30 days									
	6 months									
	1 year									

**ES = Effect Size*

†Adjusted by Age, sex(male), baseline QoL (i.e. SF12, FACT-C), POSSUM score, sex, BMI, diabetes, history of IHs, AAA, SSI, reoperation and stoma

Table 6: Example of cost-consequences table

	Hughes repair	Standard Mass Closure	Difference	p value
Costs impact				
Surgery cost/patient (£; 95% CI)				
Adverse events cost/patients				
Total health care cost/patient (£; 95% CI)				
Cost of hernia (£; 95% CI)				
Quality of life impact				
SF-6D changes baseline – 30 days				
SF-6D changes baseline – 6 months				
SF-6D changes baseline – 12 months`				
Health impact				
Number of hernia cases/arm				

Table 7: Summary of 'burst abdomen' by 30 days after the surgery

	Hughes Method	Standard Method	p-value	z value (Pr(>|z|))
Post-operative 'burst abdomen' by 30 days after the surgery	n (%)	n (%)		

Table 8: Logistic Regression Model for factors influencing risk of IH

Parameters	Coefficient (B)	df	p-value	Odds Ratio = Exp(B);	95% CI of Odds ratio
Intercept					
Arms (Hughes, Standard)					
Age					
Sex (male)					
BMI					
Diabetes					
Smoking Status					
History of IH					
AAA					
COPD					
C-POSSUM Scores					

Table 9: Cox proportional Hazard Model for factors influencing the time of developing IHs

Parameters	Coefficient (B)	df	p-value	Hazard Ratio = Exp(B);	95% CI of Hazard ratio
Intercept					
Arms (Hughes, Standard)					
Age					
Sex (male)					
BMI					
Diabetes					
Smoking Status					
History of IH					
Suture size					
AAA					
COPD					

Table 10: Prevalence of IH at one year

Time points	Hughes Method (%)	Standard Method (%)
One year		

Table 11: Summary of QoL measures over one year between with and without IH.

QoL measures	Time points	Patients with IH (n, Mean score)	Patients without IH (n, Mean score)	p-value	t-test statistic (Pr(>|t|))
SF12	Baseline				
	30 days				
	6 months				
	1 year				
FACT-C	Baseline				
	30 days				
	6 months				
	1 year				

Table 12: Prevalence of IH for 2-5 years

Time points	Hughes Method (%)	Standard Method (%)
2 years		
3 years		
4 years		
5 years		

Table 13: Summary of QoL measures (2 -5 years).

QoL measures	Time points	Hughes Method (n, Mean score)	Standard Method (n, Mean score)	p-value	t-test statistic (Pr(>|t|))
SF12	2 years				
	3 years				
	4 years				
	5 years				
FACT-C	2 years				
	3 years				
	4 years				
	5 years				

Table 14: Mean changes and effect sizes of QoL measures for 2-5 years

QoL measures	Time points	Hughes Method			Standard Method			Difference		
		n	Mean Change	ES*	n	Mean Change	ES*	Difference	95% CI	ES*
SF -12 score†	2 years									
	3 years									
	4 years									

	5 years									
FACT - C†	2 years									
	3 years									
	4 years									
	5 years									

**ES = Effect Size*

†Adjusted by Age, sex(male), baseline QoL (i.e. SF12, FACT-C), POSSUM score, sex, BMI, diabetes, history of IHs, AAA, SSI, reoperation and stoma

Table 15: IHs Diagnosis Clinical Examination vs CT image

		IHs by CT Image		
		Positive	Negative	Total
IHs by Clinical Examination	Positive			
	Negative			
	Total			

Table 16: Sensitivity and Specificity of CT image

	Values (%)	Confidence Interval (%)
Sensitivity		
Specificity		
Positive Predictive Value		
Negative Predictive Value		

Table 17: Summary of QoL measures by arms for 2-5 years.

QoL measures	Time points	Hughes Method (n, Mean score)	Standard Method (n, Mean score)	p-value	t-test statistic (Pr(>|t|))
SF12	2 Years				
	3 Years				
	4 Years				
	5 Years				
FACT-C	2 Years				
	3 Years				
	4 Years				
	5 Years				

Table 18: Summary of QoL measures between with and without IH for 2-5 years.

QoL measures	Time points	Patients with IH (n, Mean score)	Patients without IH (n, Mean score)	p-value	t-test statistic (Pr(>|t|))
SF12	2 Years				

	3 Years				
	4 Years				
	5 Years				
FACT-C	2 Years				
	3 Years				
	4 Years				
	5 Years				

Table 19: Summary of reported serious adverse events (SAEs)

	Hughes repair (n (%))	Standard Mass Closure (n (%))	Number of SAEs (n)
SAEs			
Patients			

Table 20: Seriousness criteria including death and life-threatening (LT)

	Hughes repair (n)		Standard Mass Closure (n)		Total (n)
Seriousness Criteria	**SAEs**	**Patients**	**SAEs**	**Patients**	
Death					
Life-threatening					
Hospitalisation					
Disability of incapacity					
Other medically important condition					

Table 21: List of SAEs types by arms

SAE Types	Hughes repair (n)				Standard Mass Closure (n)			
	SAEs	Patients	LT	Death	SAEs	Patients	LT	Death
Respiratory disorders (e.g. chest infection, pneumonia)								
Gastrointestinal disorders (e.g. bowel obstruction, paralytic ileus)								
Genito-urinary disorders (e.g. acute kidney injury,								

urinary tract infection)								
Wound complications (e.g. wound infection, incisional hernia)								

LT = Life Threatening

Note: The SAE types are not limited to the above four categories as these are used as examples and we are expecting more during the analysis.

Table 22: Grading of SAEs using the Clavien-Dindo Classification

SAE/Surgical Complications	Hughes repair (n)	Standard Mass Closure (n)	Total (n)
Grade I			
Grade II			
Grade IIIa			
Grade IIIb			
Grade IVa			
Grade IVb			
Grade V			
Total			

Table 23: Summary of related and suspected unexpected serious adverse reactions (SUSARs)

	Hughes repair (n)	Standard Mass Closure (n)	Total (n)
Number of related events			
Number of SUSARs			

Table 24: Summary of Wound related Complications

Wound related Complications	Hughes repair (n)	Standard Mass Closure (n)	Total (n)
Infection			
Dehiscence			

9. References

BEECHAM J., K. M. 1997. *Client service receipt inventory. Available at:* http://www.dirum.org/assets/downloads/634462388066137028-CSRI.pdf [Online]. [Accessed 16 March 2016].

BRIGGS, A., CLARK, T., WOLSTENHOLME, J. & CLARKE, P. 2003. Missing .... presumed at random: cost-analysis of incomplete data. *Health Economics,* 12**,** 377-392.

CORNISH, J., HARRIES, R. L., BOSANQUET, D., REES, B., ANSELL, J., FREWER, N., DHRUVA RAO, P. K., PARRY, C., ELLIS-OWEN, R., PHILLIPS, S. M., MORRIS, C., HORWOOD, J., DAVIES, M. L., DAVIES, M. M., HARGEST, R., DAVIES, Z., HILTON, J., HARRIS, D., BEN-SASSI, A., RAJAGOPAL, R., HANRATTY, D., ISLAM, S., WATKINS, A., BASHIR, N., JONES, S., RUSSELL, I. R. & TORKINGTON, J. 2016. Hughes Abdominal Repair Trial (HART) – Abdominal wall closure techniques to reduce the incidence of incisional hernias: study protocol for a randomised controlled trial. *Trials,* 17**,** 454.

HUGHES, B. R. & WEBSTER, D. 2011. Leslie Ernest Hughes OBITUARY. *British Medical Journal,* 343.

KHARROUBI, S. A., BRAZIER, J. E., ROBERTS, J. & O'HAGAN, A. 2007. Modelling SF-6D health state preference data using a nonparametric Bayesian method. *Journal of health economics,* 26**,** 597-612.

RUSSELL, D., HOARE, Z. S. J., WHITAKER, R., WHITAKER, C. J. & RUSSELL, I. T. 2011. Generalized method for adaptive randomization in clinical trials. *Statistics in Medicine,* 30**,** 922-934.

RUSSELL, I., ATTWOOD, S., BARR, H., EDWARDS, R. T., GLIDDON, A., INGLEDEW, D., PARK, K., RUSSELL, D., YEO, S. T., WHITAKER, R. & TEAM, C. T. 2010. CANCER OF OESOPHAGUS OR GASTRICUS-NEW ASSESSMENT OF TECHNOLOGY OF ENDOSONOGRAPHY: FINDINGS. *Journal of Epidemiology and Community Health,* 64**,** A36-A37.

SHUKLA, V. K., GUPTA, A., SINGH, H., PANDEY, M. & GAUTAM, A. 1998. Cardiff repair of incisional hernia: A University hospital experience. *European Journal of Surgery,* 164**,** 271-274.

WARD, W. L., HAHN, E. A., MO, F., HERNANDEZ, L., TULSKY, D. S. & CELLA, D. 1999. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. *Quality of Life Research,* 8**,** 181-195.