UK Cohort study to Investigate the prevention of Parastomal Hernia
The CIPHER Study
(Phase B)

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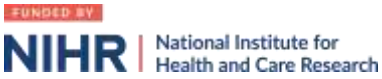


Glossary / abbreviations

ACPGBI	The Association of Coloproctology of Great Britain and Ireland
BTC	Bristol Trials Centre
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computerised Tomography
EHS	European Hernia Society
HES	Hospital Episode Statistics
HRQoL	Health-related Quality of Life
ICH-GCP	International Conference for Harmonisation of Good Clinical Practice
ICU	Intensive Care Unit
IEP	Image Exchange Portal
ISRCTN	International Standard Registered Clinical Trial Number
MDT	Multi-Disciplinary Team
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ONS	Office of National Statistics
PIL	Patient Information leaflet
PPI	Patient Public Involvement
PSS	Patient Social Services
PROs	Patient Reported Outcomes
PSH	Parastomal Hernia
QALY	Quality-adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SCN	Stoma Care Nurse
SMG	Study Management Group
STCs	Surgical Trainee Collaboratives
SSC	Study Steering Committee

1. Study summary

During abdominal surgery, it is sometimes necessary to create a stoma to divert faeces from the bowel into an external pouch or bag. Unfortunately, the formation of the stoma can be associated with future complications, including the risk of developing a parastomal hernia (PSH). A PSH is an incisional hernia, immediately adjacent and related to the stoma, that occurs when the fascia in the abdominal wall splits. Contents of the abdomen, e.g. fatty tissue or intestine, can be forced through the split in the fascia causing a bulge in the skin. PSH are relatively common and affect approximately 40% of patients within 2 years of their bowel surgery.

Complications of PSH can be severe and are known to negatively influence patients' quality of life. Specifically, PSH can make it difficult to attach stoma bags which can cause the bag contents to leak and smell, irritate the surrounding skin and make patients anxious and avoid social situations. PSH can also cause pain and serious problems, e.g. bowel obstruction, which need emergency treatment in hospital. PSH are difficult to manage and in most cases treatment involves specialist stoma care with expensive appliances. In some cases, a surgeon may reoperate to repair the hernia but additional surgery is risky and recurrence of a hernia is not uncommon. Therefore, it is very important to prevent a PSH forming in the first place.

Both patient and surgical factors are believed to influence the development of PSH. Of the surgical factors, the size and shape of the incision in the body wall, the use of mesh when the stoma is formed and, if mesh is used, exactly how it is used, have all been described as potentially important considerations. However, the way in which surgeons create stomata is very varied and research is needed to investigate whether these factors influence the risk of developing a PSH. This is the aim of the CIPHER study.

2. Background

2.1 The clinical problem

The prevalence of all types of abdominal stomata in the UK is about 100,000 and 20,000 new stomata are created annually [1]. However, the incidence of PSH is more difficult to assess due to a lack of prospective data and heterogeneity in how clinical and symptomatic PSH are defined. In the current literature, rates of PSH of up to 40% have been reported, varying according to follow-up duration, stoma type and diagnosis method.

To date a variety of methods have been used to diagnose PSH both clinically and symptomatically. Clinically, PSH has been diagnosed from intra-operative findings, clinical examination and computerised tomography (CT). Clinical examination has poor inter-observer reliability [2] and the European Hernia Society (EHS) considers CT to be best way to detect PSH when following up patients with stomata [3]. However, an 'anatomical' PSH detected by CT may not cause symptoms. Symptomatic PSH have typically been identified from health-related quality of life (HRQoL) assessments but the appropriateness of using particular HRQoL tools to detect problems specific to PSH is uncertain. Regardless of the method of clinical or symptomatic diagnosis, PSH can have substantial physical, psychological and economic consequences.

2.2 The burden of PSH

2.2.1 The physical and psychological burden of PSH

PSH are common and are symptomatic for at least 75% of patients. Pain (35%), difficulties attaching stoma bags with associated leakage of bowel contents (28%) and peristomal skin irritation are the commonest problems [4]. Bowel strangulation, obstruction and perforation may also be related to PSH and are rare but serious [5]. In addition, PSH reduces HRQoL and causes limitations in sexual function, travel, social interaction and return to work [6]. Despite advances in stoma care, the proportion of patients with symptoms has remained largely unchanged over the past 20 to 30 years [6].

2.2.2 The economic burden of PSH

The economic impact of PSH on the NHS is poorly understood because accurate data regarding stomata are difficult and expensive to extract [7]. However, it has been reported that patients with symptomatic stoma are more likely to have increased rates of consultation with community healthcare teams [8], and increased direct costs related to stoma bags and associated products such as belts, adhesives, sprays, wipes and barrier creams. The cost of stoma bags and associated products was over £228m in 2012 in England alone [9] and costs have risen over 30% in the past 5 years. Skin irritation, one of the commonest problems associated with PSH, is estimated to cost an additional 50 Euro per patient over a 7 week treatment period [10]. The cost of bags and accessories for a patient managing a stoma effectively varies between £780 and £1800 per year; this sum can rise to £6000 per year when a PSH is present [11]. Furthermore, none of the estimated costs incorporate the expense and / or time of the approximately 600 stoma care nurses (SCNs) in the UK.

Some PSH may be repaired surgically and emergency surgical intervention is indicated in some circumstances, e.g. if a PSH causes bowel obstruction. The precise number of PSH repair procedures performed annually in the NHS is currently unknown due to variation in coding. PSH repair performed as elective surgery may be recorded alone or as part of a more complex incisional hernia repair; emergency repair may be recorded as part of a laparotomy. Regardless of coding, PSH repair is associated with significant costs including: the patient's in-hospital stay (including in critical care units), theatre time, intra-operative equipment used and the cost of mesh implants. Unfortunately, complications following PSH repair surgery are common and the hernia recurrence rate is high, leading to further interventions [12-14].

2.3 Factors influencing PSH development

It is presumed that both surgical factors and patient characteristics can influence the risk of developing PSH. Patient characteristics such as diabetes, obesity and smoking have been linked with compromised tissue healing and, therefore, place patients at a greater risk of PSH. Such factors are also extremely challenging to modify. Surgical factors also have the potential to influence the development of PSH and are more amenable to modification. Such factors may include: the surgical approach (open or laparoscopic); the size, shape and site of the trephine incision in the abdominal wall; route of placement of the bowel

(extraperitoneal or transperitoneal); the use or not of prophylactic mesh at the stoma site and, if mesh is used, how it is used [15].

Of the technical surgical elements elicited above, the use of prophylactic mesh is one of the more widely studied, being the subject of 12 systematic reviews [16-26] and value analyses [27]. The systematic reviews reported that mesh use (compared with no mesh) during initial stoma formation was associated with a lower incidence of PSH. However, it is important to note that the early reviews [24-26] included the same single centre RCTs [28-30], which had methodological limitations. Specifically, these RCTs were small, had limited generalisability, were poorly designed, used different meshes with variable stomata types, varied in follow-up duration and were all at high risk of bias. Subsequent reviews have included more RCTs and concluded similarly that prophylactic mesh results in lower incidence of PSH. However, even the newer RCTs have significant methodological limitations [31] and the findings of these reviews should be interpreted with caution. Better quality multicentre RCTs with longer follow up are ongoing in Europe (PREVENT, STOMA MESH, STOMA CONST).

The costs of mesh vary according to type (e.g. biological mesh for one operation costs about £1000, synthetic mesh less than £20) but, if the more expensive option reduces the risk of PSH or the risk of complications, the post-operative costs should be reduced and a better patient outcome secured. Therefore, it is important to establish the balance of costs and benefits between options for key surgical steps.

The use of prophylactic mesh has also been subject to value analyses which reported that bioprosthetic mesh used during initial stoma construction may be cost effective at reducing the risk of PSH, if the risk of subsequent PSH repair is in excess of 39% [27]. The use of prophylactic synthetic mesh compared to no prophylactic mesh is also associated with lower costs and more Quality Adjusted Life Years (QALYs) for patients with stages I to III rectal cancer but the benefits for patients with stage IV cancer are marginal [32]. However, these conclusions are based on the results of meta-analyses of the effectiveness of mesh, which are themselves uncertain due to the small sample sizes and poor quality of the included trials.

In summary, modification of the technical aspects of surgery may reduce the incidence of PSH and could lead to improvements in the health of patients, better quality of life, a reduction in direct stoma appliance and accessory costs and fewer PSH repairs. The modifications offer the potential for significant savings for the NHS as well as benefit for individual patients. Unfortunately, existing studies on surgical technique relating to stoma formation are limited by poor design and generalisability [24] and, consequently, further high quality research is urgently needed. CIPHER will attempt to address this evidence gap.

2.4 Support for the study

The Association of Coloproctology of Great Britain & Ireland (ACPGBI) has prioritised research to investigate ways to prevent PSH [33]. The high priority of the research question has also been recognised by the Colostomy Association (a patient support organisation) and by the Association of SCNs, which both support the CIPHER study.

3. Aims and objectives

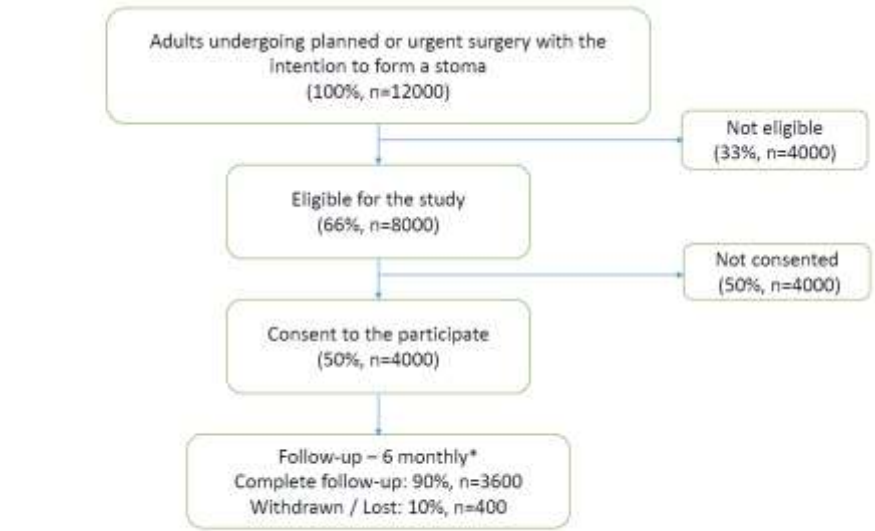
The CIPHER study (Phase B; CIPHER-B) aims to establish the incidence of symptomatic and radiologically confirmed PSH during a minimum of 2 years follow up. Additionally, CIPHER aims to evaluate the effects of key technical surgical steps during index stoma formation on the risk of subsequent PSH formation.
Specific objectives of CIPHER-B are:

1. To describe the incidence of PSH formation within 2 years of formation of all types of stomata;
2. To describe the risk of PSH for different types of stoma (end colostomy versus loop colostomy versus end ileostomy)
3. To describe the risk of PSH according to how the stoma trephine is created in the anterior fascia of the abdominal wall with respect to location (within or without the rectus sheath) and shape (cross versus circle versus slit);
4. To describe the relative risk of PSH following index stoma creation with or without mesh (no prophylactic mesh versus biologic mesh versus synthetic mesh);
5. To describe the relative risk of PSH following index stoma creation with prophylactic mesh according to mesh position (intra-abdominal versus sublay/retrorectus versus. onlay);
6. To describe the relative risk of PSH with different trephine shapes in the mesh (circle versus cross versus slit versus none (Sugarbaker)).
7. To estimate the cost effectiveness of commonly used types of mesh (e.g. biologic, synthetic) versus no prophylactic mesh in prevention PSH and improving health related quality of life.

4. Plan of Investigation

4.1 Study schema

Figure 1: The study schema for CIPHER (Phase B)



*Recruiting sites carry out participant follow up and participants are asked to complete follow up questionnaires for a minimum of 2 or until the end of the study.

4.2 Study design

This is a multi-centre, pragmatic cohort study to follow-up participants from the date of index stoma formation surgery. Follow-up will continue for a minimum of 2 years post-operatively, until closure of the cohort or death.

4.3 Setting

We intend to recruit at least 70 NHS acute trusts across the United Kingdom over a period of 12 months.

4.4 Study population

The target population is adults (18+ years) undergoing elective or expedited surgery, i.e planned operation, with the intention to form a stoma, irrespective of the primary indication for the planned surgery (e.g. colorectal cancer, inflammatory bowel disease).

4.4.1 Inclusion criteria

A participant may take part in the study if **ALL** of the following apply:

1. Aged 18 years or over
2. Able to give written informed consent
3. Undergoing elective or expedited surgery (NCEPOD Classification) to create a stoma; either an ileostomy or colostomy

4.4.2 Exclusion criteria

A participant may not enter the study if **ANY** of the following apply:

1. Lacking the capacity to consent
2. Having urgent or immediate surgery (NCEPOD Classification)
3. Previous abdominal wall stoma
4. Life expectancy <12 months from the index procedure
5. Having surgery with intention of forming a double-barrelled stoma
6. Having surgery with intention of forming a urostomy

4.5 Interventions and other predictors of outcome to be studied

Phase A of the CIPHER study (REC reference: 16/EM/0155) has defined the key surgical steps of interest. These are:

1. Method of forming the stoma trephine;
2. Whether, and how, mesh is used to reinforce the stoma trephine;
3. Use of the stoma as a specimen extraction site;
4. Closure of other wounds formed during the procedure;
5. Spouting the stoma lumen.

Details of specific data items are shown in

Table 1.

Table 1: Key surgical steps of interest

1. Trephine Formation
Subcutaneous tissue excised
Relationship of the muscle layer incision to the rectus abdominis
Anterior sheath: was a laparoscopic trocar used to puncture the anterior sheath
Size of incision [widest diameter in mm]
Shape of incision
Was any of the anterior sheath removed
Adjustments made to the size of the incision
Sutures used to buttress end of incision
Posterior sheath: was a laparoscopic trocar used to puncture the anterior sheath
Size of incision [widest diameter in mm]
Shape of incision
Was any of the posterior sheath removed
Adjustments made to the size of the incision
Sutures used to buttress end of incision
Muscle fibres separated with blunt dissection
Intra-operative vessel damage - epigastric vessel
Location of trephine in relation to port site (Laparoscopic procedures only)
Reinforcing the Stoma Trephine with Mesh
2. Reinforcing the Stoma Trephine with Mesh
Was mesh used to reinforce stoma trephine
Mesh product code
Mesh cut or adjusted
Diameter of mesh inserted if changed from original [in mm]
Shape of mesh inserted if changed from original
Location of mesh placement
Route used to position mesh
What shape was the keyhole
What size was the keyhole [in mm]
Mesh secured to abdominal wall (including sheath, muscle, peritoneum)
Mesh secured to stoma serosa
3. Use of the Stoma as a Specimen Extraction Site
Stoma trephine used as an extraction site
4. Closure of other Wounds Formed during the Procedure
Main abdominal incision
Biggest port site [in mm]
Closure of deep layer

5. Spouting the Stoma Lumen
Has the stoma been spouted

Participants' characteristics at baseline will be documented, consistent with the variables agreed as potentially prognostic for PSH in the Phase A consensus process when identifying important surgical variations.

SCNs will also document common complications that arise in hospital before discharge (**Table *2***). Complications can be both prognostic for PSH and a secondary outcome (see 4.6.2) reflecting short-term risks.

Table 2: Complications

Complication	Mild	Moderate	Severe
Bleeding:	Transfuse	Embolisation (IR)	Return to theatre
Infection - chest:	Antibiotic	Oxygen support	Ventilation / intensive care
Infection - urine:	First line antibiotic	Second line antibiotic	Pyelonephritis
Infection - Intra-abdominal:	Antibiotic	Interventional radiology	Laparotomy
Wound - infection at stoma site:	Antibiotic	Interventional radiology	Laparotomy
Wound - infection at other incisional site:	Antibiotic	Interventional radiology	Laparotomy
Wound - dehiscence:	Superficial (skin)	Deep (fascia)	Return to theatre
Would - seroma:	Drain on ward (aspirate)	Interventional radiology drain	Return to theatre
Wound - haematoma:	Drain on ward (remove wound clips)	Requires antibiotics	Return to theatre
Incisional hernia:	<4cm in size	≥4 and <10cm in size	≥10cm in size
Ileus:	<5 days	≥5 days, no IV feeding	IV feeding
Deep vein thrombosis:	Below the knee	Above the knee	Above the knee and extends into the vena cava
Pulmonary embolism:	Diagnosed radiologically, no effect on patient (except anticoagulant)	Endovascular intervention	Formal respiratory support / high care setting
Myocardial infarction:	Pharmacological treatment	Cath lab intervention (PCI)	ICU management
Delirium:	Occurs at night time only	Occurs at all hours	Psychiatric input required
Kidney failure:	IV fluid	Dialysis outside ICU	Dialysis in ICU
Pressure sore:	Grade 1 & 2	Grade 3/4	Surgical intervention
Permanent stroke:			Always severe
Return to theatre:			Always severe
Death:			Always severe
Anastomotic leak:	Antibiotics	Radiology intervention	Return to theatre
Anal/rectal stump dehiscence:	Antibiotics	Radiology intervention	Return to theatre
Mucotaneous dehiscence:	Superficial separation at the mucotaneous junction (MCJ), either partial or circumferential	Involvement of dermis layer leading to increase in width or depth of separation, partial or circumferential	Full MCJ separation involving fat layer, requiring primary wound dressing (stoma in cavity/moat)
Stenosis:	Tightening/narrowing of the stoma orifice, no dilation required	Ability to dilate, functioning ribbon like stool	Non-functioning, unable to dilate
Prolapse:	Variation in night and day length	Persistent increase in length, functioning	Persistent increase in length, non-functioning
Retraction:	Stoma partially retracted below skin level but manageable with stoma appliance	Stoma mucosa below skin level, managed with stoma appliance/accessory	Stoma below skin level, unable to manage with ostomy products
Ischaemia/necrosis:	Dark areas on stoma	Partial tissue death	Entire stoma cold and

			black (necrotic)
Peristomal skin problems:	<25% affected area	≥25 and <50% affected area	≥50% affected area

4.6 Primary and secondary outcomes

4.6.1 Primary outcome

The primary outcome will be PSH incidence during follow-up after index surgery to form a stoma. An incident PSH is defined as:

- Symptoms of PSH (see 5.4), *and*
- Clinical PSH, ascertained from participants' reports of having "been told by a nurse or doctor that you have a parastomal hernia" (6)

Participants will describe their PSH symptoms using a custom-designed questionnaire, the "stoma questionnaire" [34]. Symptoms will be classified as green (asymptomatic), amber (mild/moderate symptoms) or red (severe symptoms). Cut-off points for these classifications will be defined on the basis of on-going data collection. We anticipate that severe symptoms may include recurrent problems with the stoma appliance, pain, or admission to hospital with obstruction. Mild/moderate symptoms are likely to be associated with discomfort and ill-fitting appliance issues managed by the patients themselves.

At the same time as describing their PSH symptoms, participants will also be asked: "Have you been told by a nurse or doctor that you have a parastomal hernia?" "Yes" answers to this question will be considered to represent a clinical PSH.

The primary outcome is redefined in this version of the protocol. Anatomical PSH was previously defined on the basis of assessment of CT scans carried out in the course of a patient's usual NHS care. This amendment has been made because the study has been unable to assess all CT scans obtained for the study due to circumstances outside the control of the researchers. We remain committed to the original intent, namely that the primary outcome should reflect PSHs that "matter to patients" (and which are likely to cause additional NHS resource use, noting that there is no universally accepted definition of PSH). (See CIPHER_Protocol_v4.0.pdf for details of the previous definition.) The CT scan archive, containing approximately 6,000 scans from CIPHER participants, represents an important research resource. The research team will seek a separate favourable opinion from a NHS research ethics committee to maintain the archive and assessment software for future research.

4.6.2 Secondary outcome measures

Secondary outcomes include:

1. Intensive care unit (ICU) stay (days) during admission for index surgery
2. Hospital stay (days) during admission for index surgery and associated costs
3. Surgical site infection during admission for index surgery and 30 days afterwards
4. Other complications, documented using the Clavien Dindo classification [35] and the Comprehensive Complication Index [36, 37]

5. Questionnaire to assess symptoms of PSH (developed in Phase A; REC 16/EM/0155)
6. PSH identified from CT scan assessment
7. Generic health status (EQ-5D-5L, SF12 [38, 39]), which will be combined with survival to estimate QALYs
8. Appointments with SCNs, stoma care products used and associated costs
9. PSH repair (procedure codes for stoma formation in HES, information from SCNs) and associated hospital costs
10. Estimated cost of hospital care during follow up and primary care, social care and societal costs associated with stoma.

4.7 Justification of target sample size

The target sample size currently assumes an attrition rate of 10% at two years after index surgery. The power of the study will be increased by follow-up longer than two years for a proportion of participants and decreased by follow-up shorter than two years for a proportion (e.g. due to mortality, participants requesting to withdraw, or closures of loop ileostomies). These factors will be monitored as data accrue, their consequences for the target sample size will be modelled and the target sample size revised if appropriate.

We have estimated the hazard ratio that the study will be able to detect for a range of scenarios. The incidence of PSH is unknown; we have considered incidences of 30% and 40% as plausible. Surgical methods of interest are used with varying frequencies and so we have considered the impact of a range of ratios for the use of technical variation when comparing one variation with another, i.e. ratios of 1:1, 1:2, 1:5, 1:10 and 1:20. The correlation of the exposure of interest with other covariates is also unknown and we considered the impact of a range of correlations (0, 0.3 and 0.5). The hazard ratios that can be detected from a study of 4000 participants at the 5% level (2-sided) are shown in **Table 3**. For simplicity, we have assumed a binary exposure variable. For multi-category exposures, we will assess the overall effect of the exposure; if we were to adjust the significance level from 5% to 2% to allow for comparisons between subcategories, the power reduces from 90% (80%) to 82% (68%).

This sample size justification was reviewed by the Study Steering Committee (SSC) in April 2021, when >2,400 participants had been recruited, as part of a request to the funder for a costed contract variation. The SSC had the following observations:

1. The research question is still very important to patients and healthcare professionals in the colorectal surgical and nursing community.
2. The primary research need described in the commissioning brief was to inform the research agenda for a future RCT, rather than to provide definitive estimates of the effects of different surgical technical factors during index stoma formation.
3. At the outset, the focus of the CIPHER-B protocol was insertion of mesh when forming the stoma, different types of mesh and the varied ways in which mesh can used (objectives 4-7). For reasons unconnected to the study, mesh has been used very rarely (in only 3% of index operations), and mainly by a few surgeons.

The SSC recommended immediate cessation of recruitment and focusing on following the existing cohort for the duration of the proposed extension of 18 months (now confirmed). The SSC reached this conclusion mainly due to this proposal: being at low risk from future

waves of the COVID-19 pandemic; providing evidence to inform the research agenda most quickly compared to other options. The inability of the study to address objectives 4-7 about the use of mesh, even if recruitment continued to the original target, was another factor.

Table 3: Hazard ratios detectable in the CIPHER study for a range of assumptions, based on a cohort of 4,000 participants.

Ratio of presence: absence of covariate	Squared correlation with other covariates	Incidence of PSH	Hazard ratio detectable	
			90% power	80% power
1:1	0 (i.e. unadjusted)	40%	1.18	1.15
	0.3		1.21	1.18
	0.5		1.26	1.22
	0 (i.e. unadjusted)	30%	1.21	1.18
	0.3		1.25	1.21
	0.5		1.30	1.26
1:2	0 (i.e. unadjusted)	40%	1.19	1.16
	0.3		1.23	1.19
	0.5		1.28	1.23
	0 (i.e. unadjusted)	30%	1.22	1.19
	0.3		1.27	1.23
	0.5		1.32	1.27
1:5	0 (i.e. unadjusted)	40%	1.24	1.21
	0.3		1.30	1.25
	0.5		1.36	1.30
	0 (i.e. unadjusted)	30%	1.29	1.24
	0.3		1.35	1.30
	0.5		1.43	1.36
1:10	0 (i.e. unadjusted)	40%	1.33	1.28
	0.3		1.40	1.34
	0.5		1.49	1.41
	0 (i.e. unadjusted)	30%	1.39	1.33
	0.3		1.48	1.40
	0.5		1.59	1.49
1:20	0 (i.e. unadjusted)	40%	1.46	1.39
	0.3		1.58	1.48
	0.5		1.71	1.59
	0 (i.e. unadjusted)	30%	1.55	1.46
	0.3		1.69	1.57
	0.5		1.86	1.71

4.8 Measures taken to avoid bias

Measures taken to protect against bias are described below in relation to the bias domains potentially affecting non-randomized studies of interventions [40]:

i. Bias due to confounding

Two extremes of practice are possible:

(a) surgeons prefer some variants in surgical technique to others and apply their preferred variant to all of their patients, irrespective of the patients' characteristics;
(b) surgeons use several variants in surgical technique and choose the variant for a particular patient according to the patients' characteristics or other factors.

In situation (a), we expect that the risk of bias due to confounding will not be a serious issue since all surgeons are likely to operate on a wide variety of patients, i.e. predictors *other than* variations in the way a surgeon creates a stoma will be distributed similar within all surgeons; if (a) can be shown, there is also the possibility of adjusting for potential predictors other than surgical variations using an instrumental variable, i.e. surgeon preference one or other surgical method [41]. In situation (b), the risk of bias due to confounding will be potentially serious and we are likely to have to control for confounding by conventional, multivariable methods since an instrumental variable is unlikely to be available. We will be able to distinguish between situations (a) and (b) on the basis of the surgical data accruing as the study progresses.

ii. Bias in selection of participants into the study (selection bias)

Bias in selection of participants cannot affect the cohort study because we will study an inception cohort from the date of index surgery, carefully applying the eligibility criteria for the study without selection.

iii. Bias in the measurement of interventions (misclassification bias)

Bias in measurement of the interventions, i.e. the key surgical steps, will be minimised by the careful definition of these steps as achieved through Phase A of the CIPHER study (see **Table *1*: Key surgical steps of interest**). These definitions have been applied when designing the electronic case report form (e-CRF) that will be completed with reference to the lead surgeon scrubbed at the time of stoma formation, before a participant leaves the operating theatre.

iv. Bias due to departure from intended interventions (performance bias)

Performance bias will be minimised by estimating the effects of the key surgical factors that were *intended* to be implemented [42].

v. Bias due to missing data (attrition bias)

Bias due to missing data will be minimised by using multiple methods to collect the data needed for the study (see 5.4), especially data relating to the follow-up of participants (see 5.4).

vi. Bias in the measurement of outcomes (detection bias)

We do not expect measurements of patient-reported PSH symptoms and other patient-reported outcomes (PROs) to be at risk of bias, since participants are unlikely to know the surgical methods used when forming the index stoma or the comparisons of interest; moreover, it is very unlikely that they have expectations about the potential influence of variations in the surgical methods on outcome. SCNs collecting outcomes in hospital or during follow-up after discharge will not know the surgical methods used; assessors grading CT scans (i.e. assigning an EHS class and 'scoring' other anatomical signs of PSH) will also not know the surgical methods used.

vii. Bias in selection of the reported result (reporting bias)

Bias in selection of the reported results will be minimised by: (a) registering the study, including a description of the key elements of the research questions being addressed, on a publicly accessible registry (e.g. ISRCTN); (b) finalising a detailed statistical analysis plan (SAP) before locking the database for the study; (c) adhering to the SAP wherever possible and documenting any deviations with reasons when deviations are required due to unforeseen circumstances.

5. Study methods

5.1 Participant recruitment

The care of patients undergoing large and small bowel elective surgery for cancer or for inflammatory bowel disease is co-ordinated in all centres by specialist multi-disciplinary teams (MDTs). The MDTs meet regularly and consider all patients on the basis of their relevant staging investigations and other assessments. As part of usual care, a SCN or a surgeon will meet a patient identified by the MDT as requiring resection and stoma formation before surgery. The SCN or surgeon will give information about the study (patient information leaflet, PIL) to potential participants. Patients will be given as long as possible to consider the study before being approached for consent (at least 24 hours for elective surgery and usually more than 24 hours for expedited surgery). On rare occasions when a theatre becomes unexpectedly available, patients undergoing expedited surgery may be asked for consent less than 24 hours after receiving information about the study. SCNs approaching patients will not consent a patient if he/she requests longer thinking time and this was not available; patients who are visibly distressed will not be approached for consent.

Patients may be consented retrospectively following their surgery, as well as prospectively. Retrospective consent will be sought from eligible patients when consent cannot be obtained preoperatively for example: when a final decision to form a stoma is not made until the patient is in theatre; and when there is not enough time to discuss or for patients

to consider the study fully prior to surgery. Wherever possible, the patient will be informed about the study prior to their surgery.

We aim to recruit at least 70 NHS Trusts over a 12 month period. Participants will be recruited over 24 months. We anticipate that about 12000 patients will be screened during this period, that 66% (n ≈ 8000) will be eligible and that 50% (n ≈ 4000) of eligible patients will consent to take part in the study. This equates to a recruitment rate of about 4 patients per centre / per month, although this average number will vary according to the workload of a centre. The proposed schema is shown in **Figure 1**.

Recruitment was reviewed by the SSC in April 2021, when advising about a request to the funder for a costed contract variation. In addition to slower than expected recruitment of sites and participants since the outset, recruitment to the study was paused at most sites from March 2020 due to the COVID-19 pandemic, and only 443 participants were recruited between then and May 2021. The total number recruited at 22nd May was 2440. After discussion with the SSC (above), the CIPHER study team applied to the NIHR to end recruitment on 30th June 2021. The main reason for making this recommendation was that CIPHER was primarily designed to inform the future research agenda for preventing PSH, rather than to provide definitive estimates of the effects of particular surgical steps. The current sample is sufficient to do this. The NIHR agreed with this decision and to a funded extension to allow continued follow up the existing cohort for a further 15 months from 1st July 2021.

5.2 Research procedures

Patients will undergo stoma formation in accordance with the techniques habitually used by each participating surgeon. The details of the procedure and aftercare will be at the discretion of the surgeon and in accordance with usual practice at each participating centre.

Research procedures for the purposes of the study only include:

- Provision of study information, review of the eligibility criteria and invitation to eligible patients to consent;
- Collection of key baseline, intraoperative and post-operative data for participants;
- Completion by participants of follow-up questionnaires, at the intervals specified in **Table 3**;
- Requests for participants' CT scans carried out in the course of usual care during the follow-up period.

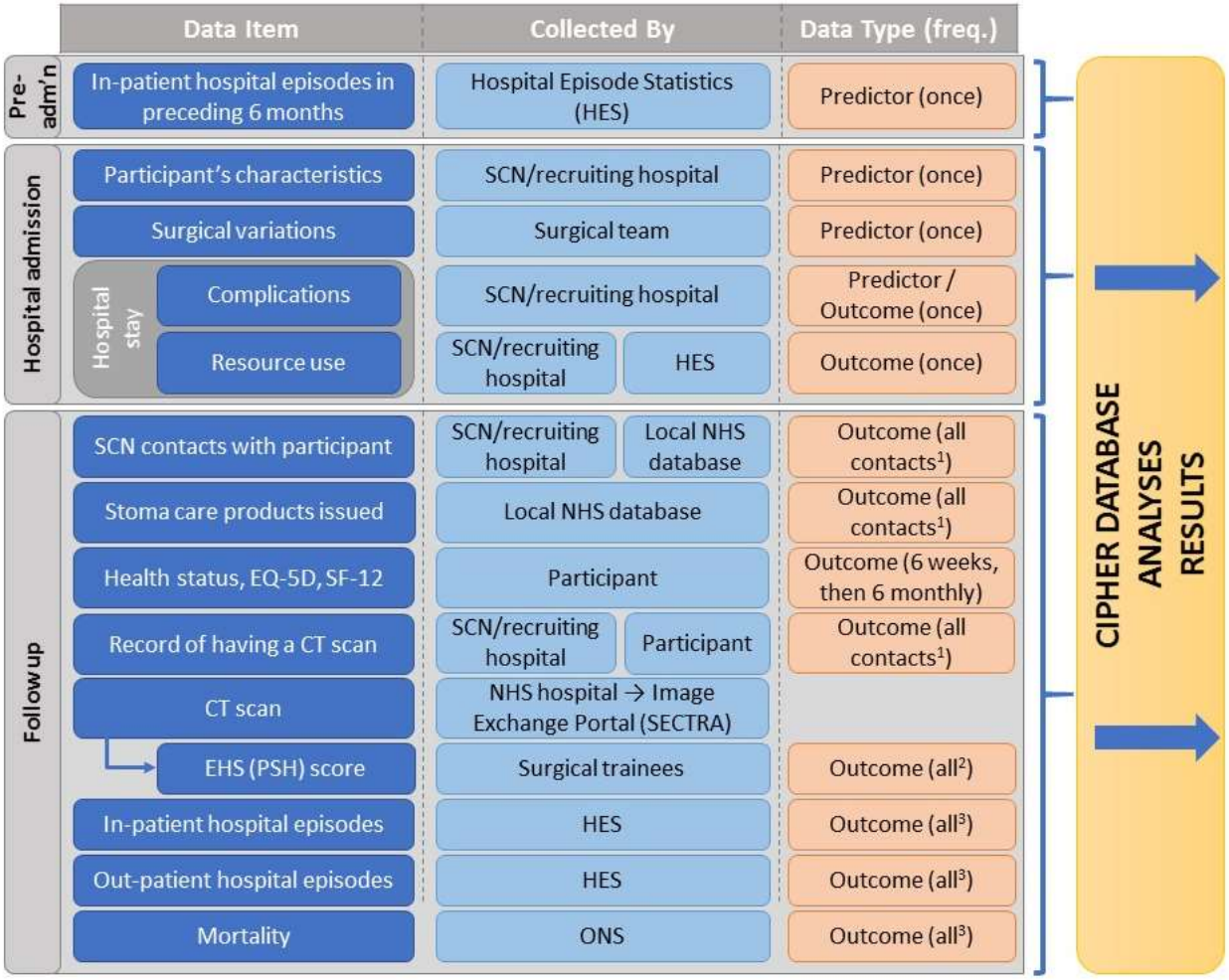
5.3 Definition of end of study

Patients who consent to the study will be followed-up with patient questionnaires for a minimum of 2 years post-operatively. The end of the study will be the point in time when the last participant enrolled completes their 2 year questionnaires, all database queries have been resolved and the database has been locked.

5.4 Data collection

Data will be captured in a purpose-designed secure database. Data required for the cohort study will be collected at different times (and by different people; see **Figure 2**). Additional details of specific data items are shown in **Table 4**.

Figure 2: Data Collection Diagram



Footnotes:

1. SCNs will record the number of visits at 6 weeks, 6 months and 6 monthly thereafter; we also intend to obtain these data from the database used locally.
2. We intend to obtain data for all visits from the database used locally.
3. HES and ONS data should record all hospital activity but will only be extracted at the end of the study.

Table 4: Timing and frequency of collection of data items

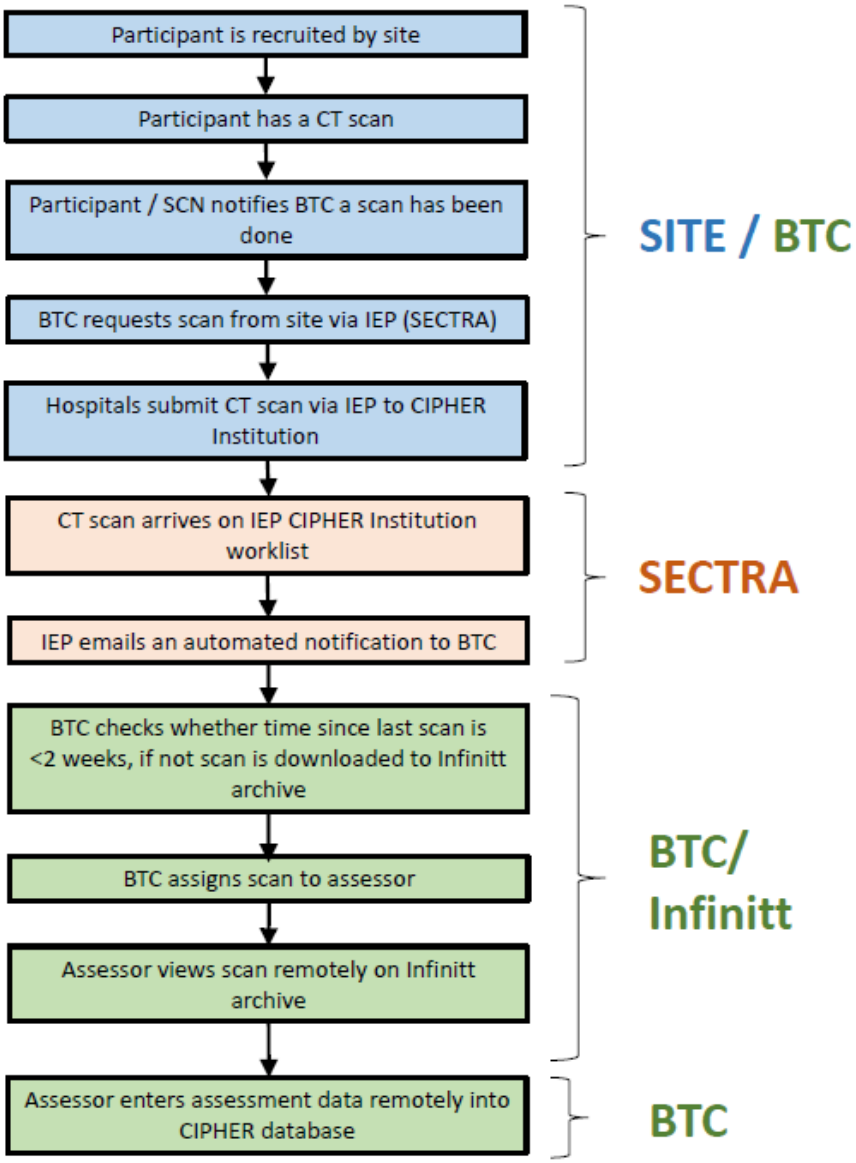
	Time / frequency of data collection with respect to date of index surgery						
	Before	**During**	**Up to discharge**	**6-weeks after**	**6-month after**	**12-month after**	**6-monthly to study end**
Screening log	✓						
Consent form	✓						
Participant baseline details	✓						
Surgical details		✓					
Complications			✓				
Index hospitalisation resource use		✓	✓				
SCN contacts with participants and hospital admissions				✓	✓	✓	✓
Exercise, support garment data				✓	✓	✓	
EQ-5D-5L; SF-12	✓			✓	✓	✓	✓
Wound questionnaire			✓	✓			
Community-based health care					✓	✓	✓
Stoma questionnaire					✓	✓	✓
Questionnaire about living with a stoma						✓	
Request CT scans, taken as part of patient's usual care				✓	✓	✓	✓
Stoma care products issued				✓	✓	✓	✓
In-patient hospital episodes *					✓	✓	✓
Out-patient hospital episodes *					✓	✓	✓

Footnotes:
*In-patient and out-patient hospital episodes will be extracted from HES data, which will be requested at the end of the study.

Data collection will include the following elements:

(a) A screening log of patients undergoing elective surgery to form a stoma. This log will be maintained by centres but data from the log will only be entered for eligible patients who consent to take part in the study (i.e. participants).
(b) Confirmation of patient's eligibility against all eligibility criteria, written informed consent and patient's contact preferences (see below).
(c) Baseline data characterising participants before surgery will be collected by the SCNs and obtained retrospectively from a HES data extract. Data from these sources will include any relevant diseases and comorbidities the participant may have and their current health status.
(d) Surgery details will be collected by the surgical team in theatre and entered into an online database. These details will describe how the stoma is formed.
(e) Details of a participant's recovery after surgery will be collected at discharge by the SCNs and obtained retrospectively from a HES data extract. These details will describe the patients post-operative stay including surgical or medical complications.
(f) All follow up contacts between a participant and a SCN will be recorded by the SCNs; we also intend to obtain these details from local NHS stoma care databases used by hospitals when available.
(g) Participants will be asked to complete health questionnaires, i.e. the EQ-5D-5L and SF-12, a purpose-designed questionnaire about stoma symptoms developed in Phase A [34], a questionnaire about how the participant is adapting to living with a stoma [43] and brief questions about primary care, social care and other resource use related to the stoma. Participants will be able to choose to receive the questionnaires by post or to complete them via an online secure website. Subject to their consent, we may also issue reminders to participants about completing questionnaires by text messaging.
(h) CT scan images performed during the patient's involvement in the study will be obtained through the image exchange portal (IEP). These images will be assessed by surgical trainees using the European Hernia Society (EHS) classification system (see **Figure 3**). Our intention is to review at least one CT scan during each year of follow-up. The frequency of CT scans may also indicate that a participant has a health problem and the coordinating team will monitor this. A CT scan taken less than 2 weeks after the previous scan will not be requested for assessment.
(i) Information about in-patient hospital episodes and out-patient hospital episodes will be obtained at the end of the study from linked extracts of Hospital Episode Statistics (HES) data, from NHS Digital.
(j) Information about participants who die during the study will be obtained at the end of the study from linked data extracts from the Office of National Statistics (ONS).
(k) Information about resource use will be collected from participants directly (to record primary and social care use), from routinely collected data sources, e.g. NHS Digital (hospital episode statistics) and database used locally to record SCN visits and stoma care products issued.

Figure 3: Data flow for CT scans



5.5 Assessment of CT scans

Volunteer surgical trainees (members of Surgical Trainee Collaboratives, STCs) will be recruited to assess CT scans (see section 6). They will be trained (see section 7) to grade CT scans using the EHS PSH classification and to assess other features; as part of training, a trainee will have to pass a performance assessment, comparing his/her grading with the grading of an expert. The process by which such patients and their scans will be identified and managed is described in **Figure 3**.

CT scan grading by trainees will be carried out in duplicate, using a web application developed for the study. CT scans will be requested via IEP (Sectra Ltd) and then transferred to a secure archive hosted by Infinitt UK Ltd where they will be viewed. Data will be pseudoanonymised on transfer to the Infinitt archive (identifiable information in scan

headings removed) and identified by the participant study ID. When duplicate trainee classifications differ on key features, e.g. presence of PSH, the CT scan will be adjudicated by an expert assessor. Duplicate grading will also provide information about the reproducibility of all graded features.

The features to be graded are:

- incisional hernia visible (Y/N)
- maximal axial diameter of the trephine (cm/mm)
- maximal craniocaudal diameter of the trephine (cm/mm)
- type of tissue involved in the hernia
- volume of tissue involved in the hernia
- amongst other things.

5.6 Source data

Source data will include all questionnaires completed by the patient during their involvement in the study. The patient's medical notes will be considered as the source for data collected on paper CRFs (most baseline and post-operative data during the index admission, and 6 weeks, 6 months and subsequent 6 monthly contacts with a SCN). The source for surgical details will be the data entered into the e-CRF (these are not routinely collected in medical records or operation notes).

Results of any scans, particularly CT, will be considered as source data for those patients that undergoing imaging to assess PSH. Finally, additional HES data will be extracted, which will be considered as source data.

5.7 Selection of confounders

The challenges of confounding have been described above (see section 4.8). We will be able to inspect the accruing data to find out how participating surgeons choose particular surgical variants in relation to participants' characteristics. Assuming that analyses will need to take confounding into account by one method or another, we will consider the list of confounding factors in **Table 5.**

Table 5: List of confounding factors

1.	**Baseline Clinical Details**
	- Age
	- Anthropometry: body mass index
2.	**Medical History / Current Health Status:**
	- Diabetes
	- Chronic kidney disease
	- Previous abdominal surgery
	- Abdominal wall hernia
	- Muscular or connective tissue disorder (e.g. aneurysm disease, Ehlers-danlos syndrome, Marfan syndrome, ostergenesis imperfecta, scleroderma, rheumatoid arthritis, SLE)
	- Parity (for females)
	- Frailty score
3.	**Current Health Status**
	- Smoking history (non-smoker, ex-smoker (minimum 3 months tobacco free), current smoker)
	- Corticosteroid use within 6 months of index surgery
4.	**Neoadjuvant treatment**
	- Treatments in the last 6 months relating to the primary reason for stoma formation (e.g. diseases resection / debulking, chemoradiotheraphy, chemotherapy or radiotherapy)
5.	**Indication for Surgery**
	- Inflammatory Bowel Disease
	- Diverticular Disease
	- Functional Intestinal disorder
	- Tumour (benign or malignant)
6.	**Lifestyle and Behaviour**
	- Abdominal exercise
	- Use of support garments

Baseline confounding factors will be collected during the admission for the index surgery. One additional item collected will be information about a participant's use of abdominal exercises aimed at improving core muscles and support garments, which will be documented at 6 weeks, 6 months and 12 months by SCNs when participants have started to become used to having a stoma. Although this item relates to a period of time after the index surgery, it is not expected to be influenced by the surgical methods used, not least since participants and SCNs will not know what methods were used.

5.8 Discontinuation/withdrawal of participants from the prospective cohort study

Each participant has the right to withdraw from the study at any time. If the participant wishes to withdraw, data collected until the time of the withdrawal will be included in the analysis unless the patient specifically requests for their data to be destroyed.

5.9 Frequency and duration of follow up

Patients who consent to the prospective cohort study will be followed-up for a minimum of 2 years after their index procedure. Intervals of follow-up are specified in **Table 4**. Follow-up questionnaires will be issued by the coordinating centre (BTC).

5.10 Likely rate of loss to follow-up

In accordance with **Figure 1**, we expect that ≥90% of patients will complete follow-up or die within the minimum 2 year follow-up period, i.e. loss to follow-up of <10% for the primary outcome for reasons other than death. We will make all reasonable efforts to stay in contact with patients through the use of postal communication, email, text message and telephone. We will also use multiple sources to track participants during follow-up (see 5.4). About a further 15% are expected to die within two years; the reduced follow-up for these participants may impact on the power of the study to detect associations between PSH and surgical variants, depending on whether death occurs before or after ascertainment of a PSH. The impact of attrition due to death on the power of the study will be reviewed as data accrue to ensure that the study can address the objectives satisfactorily.

5.11 Expenses

CIPHER is an observational cohort study that involves no deviation from the standard patient care pathway. Furthermore, there is no 'intervention' and therefore no costs will be accrued by patients. Accordingly, patients will not receive any funds / expenses for taking part.

6. The Surgical Trainee Collaboratives (STCs)

The surgical trainee collaboratives (STCs) are organisations run by trainees and medical students that assist with multicentre clinical surgical research. The research team will engage with the STCs to promote the success and deliverability of CIPHER. We will develop a web application for trainees to use to grade CT scans (see 5.5). We anticipate engaging the STCs in three main capacities:

1) Validating the ability of volunteer surgical trainees to grade PSH from CT scans; this will demonstrate that STCs can be trained to read CT scans, classify scans reproducibly and validly with respect to PSH according to the EHS classification and collect additional anatomical data from the scans (see 7).
2) Reviewing CT scans of participants in the CIPHER cohort. Scans will be reviewed and assessed (by STCs) according to the EHS classification system (see 4.6.1)
3) Involvement in the recruitment of patients and collection of essential study data with particular reference to data related to intraoperative manoeuvres (see 4.5).

7. Training infrastructure for STCs

It will be necessary to train surgical trainees to assess the CT scans. Therefore, this protocol also describes the infrastructure we propose to establish to do this, since infrastructure does not exist outside the study and is required for it.

A selection of identifiable CT scans from patients with stomata have been obtained with consent by the Chief Investigator for a previous study and researchers carrying out Phase A of the CIPHER study. We will write to patients who gave permission for their CT scans to be used previously and ask their consent to use their scans in the CIPHER study to train volunteer trainees to grade CT scans. All scans for which patients give their consent will be transferred from IEP to our CT scan archive hosted by Infinitt UK Ltd .

Trainees will be directed to view a training video to learn about the feature they are required to grade and how to use the CIPHER web application to record their assessments. The training CT scans will be able to be viewed through the Infinitt UK Ltd archive, just like CT scans obtained for participants in the main cohort. A range of training scans will be queued for assessment by a trainee. When the trainee is confident about carrying out the grading, he/she will be able to request the BTC to queue a set of training CT scans. In order to be accepted as a grader for the main cohort study, a trainee will have to achieve 90% accuracy in assigning EHS PSH class, compared to the class assigned by an expert grader.

This group of patients will be similar to those recruited to the prospective cohort (having undergone stomata formation at our CI's institution) and will be approach for their consent to use their images for the purposes of STC training and assessment. A patient information leaflet will explain the study and will be sent to patients along with a postal consent form. However, a PIL and consent form will only be sent to patients, once we have confirmed their survival status on NHS Spine. This is essential because the majority of this cohort have undergone bowel resection for cancer.

8. Statistical analyses

8.1 Plan of analysis

The data will be analysed according to the intention to implement a surgical step and will be reported in accordance with the principles of the CONSORT guidelines (but not items relating to randomization). A detailed statistical analysis plan will be prepared prior to locking the database. The primary outcome, time to PSH (defined as the time when PSH confirmed by imaging) and secondary time-to-event outcomes, will be analysed using survival methods. The models will take account of the hierarchical structure of the data; i.e. participants, nested within surgeons nested within centres. The hazards of key predictors will be estimated, with 95% confidence intervals, after adjusting for important procedure, patient and surgeon confounding factors.

The factors included in the model, the modelling strategy and the approach to handling correlated covariates will be documented in the statistical analysis plan [44]. Participants

free from a PSH at final follow-up will be censored. Follow-up will also be censored if bowel continuity is restored, if participants have their stoma moved to a new site or die. These circumstances leading to censoring may be informative and sensitivity analyses (setting survival times to the longest observed times) will be undertaken to assess the potential impact of informative censoring. Secondary continuous outcomes will be analysed using a mixed regression model, again taking account of the hierarchical structure of the data and the repeated measurements over time. Binary outcomes (e.g. complications) will be analysed using logistic regression. If the frequency of the outcomes allows, these models will also take account of the hierarchical structure of the data.

In view of the very limited use of mesh in the study to reinforce stoma formation (see 4.7), analyses are likely to focus on other modifiable surgical factors.

8.2 Subgroup analyses

No sub-group analyses are planned.

8.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants, any queries on the database has been resolved and the database has been locked. No formal interim analysis is planned.

8.4 Economic analysis

The economic analysis aims to estimate the cost effectiveness of commonly used mesh types versus no prophylactic mesh in patients with stoma surgery for rectal cancer.

The economic evaluation will be a cost-utility analysis from the NHS perspective. NHS costs include those associated with (i) the operation, (ii) the post-operative inpatient stay and (iii) stoma care and PSH repair during follow-up. Unit costs for products such as mesh will be based on the purchase price at a range of hospitals participating in the study. The cost of other resources will be obtained from national sources where available.

The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs) estimated using the EuroQol EQ-5D 5L. We will conduct a model-based cost-effectiveness analysis comparing synthetic mesh, biologic mesh, and no mesh to prevent PSH—stratified by rectal cancer stage. Our analysis will synthesize evidence from the CIPHER cohort and the wider literature using a decision tree and Markov model. Specifically, (i) we will use data from CIPHER and the wider literature to estimate the baseline risk of developing asymptomatic and symptomatic PSH in patients with no mesh after the initial stoma creation; (ii) we will include recent RCTs with longer follow-up to estimate the relative risks of PSH incidence with mesh (synthetic or biologic) compared with no mesh; (iii) we will incorporate short-term cost and quality of life data from the CIPHER cohort; (iv) our analysis will use a patient lifetime horizon based on literature estimates of mesh complications, PSH repair and recurrence and mortality. We will use probabilistic analyses to estimate uncertainty in model parameters and outputs. Longer term costs and benefits

beyond the first 12 months will be discounted in line with recommendations prevailing at the time [45].

9. Study management

The trial will be managed by the Bristol Trials Centre (BTC). The BTC will prepare all the trial documentation and data collection forms, develop and maintain the study database, issue follow-up questionnaires, check data quality as the study progresses, monitor recruitment and carry out study analyses in collaboration with the clinical investigators.

9.1 Day-to-day management

The study will be managed by a Study Management Group (SMG), who will meet either face-to-face or by teleconference, every six weeks or more frequently if required. The SMG will be chaired by the Chief Investigator and will include key members of the named research team (see Chief Investigators & Research Team Contact Details).

9.2 Monitoring of sites

9.2.1 Initiation visit

Before the study commences, training session(s) will be organised by BTC . These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study. Initiation visits for the CIPHER study will comprise: face-to-face training, teleconference training or online / remote training.

9.2.2 Site monitoring

The responsibility to monitor centres participating in the CIPHER study has been delegated to the CTEU, BTC by the study sponsor. Monitoring will be conducted in accordance with the risks identified within the study risk assessment. Monitoring, either onsite or centrally, will be performed as required to ensure adherence to ICH-GCP and data collection procedures described in section 5.4.

9.3 Study Steering Committee (SSC)

A Study Steering Committee will be convened, but there will not be a Data Monitoring Committee since the study will not alter participants' care. The SSC is made up of co-applicants on the grant and independent members appointed by the funder. The independent members include surgeons, nurses and patient representatives.

The independent members include:

- Brian Stephenson (Chair), Consultant General and Colorectal Surgeon
- Darren Boone, Consultant Gastrointestinal and General Radiologist
- Aileen McKinley, Consultant Colorectal Surgeon
- Andrew Hutchings, Assistant Professor in Health Services Research
- Carol Katté, Stoma Care Nurse

- Tracey Holland, Bladder and Bowel Nurse
- John Haworth, Patient Representative
- Sarah Squire, Patient Representative

Members of the research team will attend the meetings to provide information about the study to the committee.

9.4 Patient & Public Involvement (PPI)

This study was discussed at the Association of Coloproctology of Great Britain and Ireland (ACPGBI) Patient Consultation Exercise on March 26th, 2015. Representatives of national inflammatory bowel disease, colorectal cancer, ileostomy and colostomy patient support groups discussed and prioritized 24 different research topics. The prevention and treatment of PSH were considered to be the second highest non-cancer research priority.

During the conception of this project study representatives met with patients, representatives of patient organisations (Colostomy, Ileostomy & Urostomy Associations) and professionals to garner feedback on the proposed study and to continue to engage with the PSH community. We have had patients involved in the design of the study and we have two patient representatives on the Study Steering Committee.

A PPI group will be set up including patients who have had PSH associated with different types of stoma fashioned in the treatment of both benign and malignant diseases. McNair will facilitate this group who will meet regularly to review and provide feedback on various aspects of the study such as reviewing participant documents, increasing participant recruitment and writing lay summaries. The group will also advise on methods and content of communication with participants and, after the study has ended, on dissemination of its findings to potential future patients.

10. Safety reporting

As this study does not require participants to undergo any additional investigations, it is not possible for clinical adverse events to be attributed to study specific procedures.

11. Ethical considerations

11.1 Review by an NHS Research Ethics Committee

Ethical review of the protocol and supporting documentation, including patient information sheets, consent forms and GP letters will be carried out by a UK Research Ethics Committee (REC). Furthermore, any amendments that constitute a substantial amendment will also be reviewed by the REC as appropriate.

CIPHER is a multiphase study and as such REC approvals will be obtained for each phase (A & B) separately. This protocol relates to Phase B of the study, however for completeness the REC reference for Phase A is 16/EM/0155.

11.2 Risks and anticipated benefits

11.2.1 Potential Risks

There is no additional physical risk to patients who agree to take part in this observational study because there is no deviation from standard care or operative strategy. There is a hypothetical risk that patients who develop PSH may be uncomfortable reporting symptoms of their condition on their follow-up questionnaires. However, we feel that this risk is hypothetical and will be outweighed by the potential benefits of the research to future patients and to society.

During their involvement in the study patients may undergo cross-sectional imaging (CT or MRI) for the purposes of disease surveillance or to identify the presence of PSH. Such scans *may* involve the use of ionising radiation (CT), which are associated with a small risk. However, any such scans will be part of standard care and are not study specific procedures.

11.2.2 Potential benefits:

The CIPHER study has the potential to significantly benefit society by addressing an important area of clinical uncertainty for patients at risk of developing PSH. This research priority was supported by a recent survey of the ACPGBI that ranked optimisation of methods to prevent and repair PSH as the second most important research question not related to cancer [46].

11.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

11.4 Obtaining informed consent from participants

All participants will be given or sent a Patient Information Leaflet (PIL) and the opportunity to deliberate before being approached for their written informed consent. The majority of patients, those undergoing either elective or expedited (but not urgent or immediate) surgery to form a stoma, will meet with a SCN prior to surgery, who will describe the study and address any concerns that the patients may have. In some instances, consent may be taken retrospectively following the participant's surgery. When this happens, participants will have the same opportunity to deliberate about participation before being approached for their written informed consent. If the patient declines the study, their intraoperative data will be deleted.

The member of the research team taking consent will be appropriately trained and delegated to perform their role. A copy of the signed Informed Consent form, along with a copy of the PIL will be given to the study participant to keep. Furthermore, the original

signed informed consent form will be retained for trial records and a further copy will be placed in the patient's medical notes.

11.5 Co-enrolment

Participants may be enrolled into other non-interventional studies. Ability to co-enrol into other interventional studies will be discussed with the relevant investigators.

12. Research governance

This study will be conducted in accordance with the principles of:

- The International Conference for Harmonisation of Good Clinical Practice (ICH-GCP) guidelines
- The Research Governance Framework for Health and Social Care

12.1 Sponsor approval

The original study documentation, along with details of any amendments to the study documents will be approved by the sponsor prior to submission to the REC.

12.2 NHS approval

Approval from the local NHS Trust is required prior to the start of the study at each participating centre. Furthermore, any amendments to the study documents approved by the REC will be submitted to the Trust for information or approval as required.

12.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements have been signed off by all parties before recruiting a participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved the REC that they receive and ensure that the changes are complied with.

12.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor (or delegates) policy, which is consistent with the Research Governance Framework. All study related documents will be made available on request for monitoring and audit by the sponsor (or delegates) and the relevant REC.

12.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG (96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

13. Data protection and participant confidentiality

13.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

13.2 Data handling, storage and sharing

13.2.1 Data handling

Data will be entered onto a purposed designed database. Access to the main database will be via a secure password-protected web-interface (NHS clinical portal). Surgical data will be entered on the NHS network via a generic login to allow the surgical team to enter the data. No identifiable data will be visible and only data items necessary to enable linkage in the main database will be collected (NHS number, operation date and gender). Follow-up questionnaires will be submitted to the BTC by post or the participant may choose to complete the questionnaire electronically. Participants will enter their data through a secure website of the University of Bristol; this is because participants cannot be provided with access to a database inside the NHS network.

Data will be entered promptly and data validation and cleaning will be carried out throughout the study. A study manual covering database use will be available and regularly maintained.

13.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Prior to destruction, paper records may be scanned and stored on the University server with limited password controlled access. Where study related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the study in accordance with coordinating centre policies. In compliance with the MRC Policy on Data Preservation, relevant 'meta'-data about the study and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier, and key personal identifiers (e.g. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a

physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

13.2.3 Data sharing

Patients who agree to take part in CIPHER will be asked for their consent to securely transfer their NHS number, postcode and date of birth to NHS Digital. Data concerning patient admissions and service utilisation will be sought from NHS digital to inform the cost analysis of the study.

In addition to the data sharing specified above, study data may be shared for other research (by researchers in NHS or academic institutions) relating to patients who have stomas at any time, providing the data are used for objectives that do not overlap with the CIPHER study objectives. Data relating to CIPHER study objectives may be shared for secondary research after publication of the main results. Data will only be shared where participants have agreed for it to be used in future ethically approved research. In all instances, sharing of anonymised individual patient data should be conditional on assurance from the researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the research, e.g. a study protocol or a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body.

14. Dissemination of findings

The findings will be presented at national/international conferences, published in peer-reviewed academic journals, professional media (e.g. to SCNs) and accessible formats in newsletters to patients, in accordance with advice from the PPI group about how best to do this effectively. The findings will also be reported as a briefing paper to commissioners (e.g. commissioning groups, NICE) and to other health care stakeholders with an interest in the research.

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16. Amendments to protocol

Amendment number (i.e. REC number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
SA 1	V1.0	11 October 2017	V2.0	05 November 2018	Change to eligibility criteria and addition of retrospective consent. Addition of health economic study objective.	07/12/2018
SA 3	V2.0	7 November 2018	V3.0	12th August 2021	1. Updates to recruitment and target sample size sections explaining reasoning behind closing the study before original sample size has been met. 2. Plan of analysis and economic analysis sections have been updated with more details of analysis strategies. 3. The data sharing policy has been updated with	01/09/2021

					more specific detail.	
SA 4	V3.0	12th August 2021	V4.0	4th May 2022	1. Updates to training infrastructure and CT assessment sections to reflect new viewer and archive provider. 2. Update to the collection of HES data. Only one extract will be applied for at the end of the study. 3. Sentence added to the plan of analysis section to clarify that analyses will focus on modifiable surgical factors. 4. Update to Sponsor name as they have merged with Northern Devon Healthcare NHS Trust. 5. References to CTEU replaced with Bristol Trials Centre as merger with Bristol Randomised	24/05/2022

					Trials Collaboration completed.	
SA5	V4.0	4th May 2022	V5.0	5th January 2024	1. Update to primary outcome. Change in "anatomical PSH" (one part of the original composite outcome) to "clinical PSH" (participants' reports of having "been told by a nurse or doctor that you have a parastomal hernia NHS resource use). 2. Change in Lead Statistician.	29/01/2024