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TRIAL PROTOCOL

Protocol for the UK cohort study to investigate the prevention of parastomal hernia (the CIPHER study)

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Abstract

Aim: Abdominal surgery sometimes necessitates the creation of a stoma, which can cause future complications including parastomal hernia (PSH), an incisional hernia adjacent to and related to the stoma. PSH affects approximately 40% of patients within 2 years of stoma formation. Complications of PSH reduce a patient's quality of life and can be severe (e.g. bowel obstruction). PSHs are difficult to manage and can recur after surgical repair. Therefore, it is very important to prevent a PSH. Surgeons create stomas in different ways and both patient and surgical factors are believed to influence the development of PSH. The aim of the CIPHER study is to investigate the influence of different surgical techniques on the development of PSH.

Method: The UK cohort study to investigate the prevention of parastomal hernia (the CIPHER study) aims to recruit 4000 patients undergoing elective or expedited surgery with the intention of forming an ileostomy or colostomy, irrespective of the primary indication for the planned surgery. For each patient, surgeons will describe their methods of trephine formation, mesh reinforcement of the stoma trephine, use of the stoma as a specimen extraction site and wound closure. The primary outcome will be incident PSH during follow-up, defined as symptoms of PSH (custom-designed questionnaire) and anatomical PSH, ascertained by independent reading of usual care CT scans. Secondary outcomes will include surgical site infection, the Comprehensive Complication Index, quality of life (EQ-5D-5L and SF-12), PSH repair and use of NHS resources.

Results: Results of the study will be submitted for publication in peer-reviewed journals. All publications relating to the results of CIPHER will use a corporate authorship, 'The CIPHER Study Investigators' with named writing committee members.

Conclusion: The CIPHER study will be the first to investigate detailed surgical methods of stoma formation in a large, representative cohort of patients with a range of primary indications, both cancer and noncancer.

Registration details: ISRCTN registry, identifier ISRCTN17573805.

KEYWORDS
cohort study, stoma, parastomal hernia

INTRODUCTION

Over 100 000 people in the UK currently live with a stoma, and approximately 20 000 new stomas are created every year [1]. A parastomal hernia (PSH) has been defined by the European Hernia Society (EHS) as 'an abnormal protrusion of the contents of the abdominal cavity through the abdominal wall defect created during placement of a colostomy, ileostomy or ileal conduit stoma' [2]. Surveys of patients with PSH reveal that the majority have symptoms which include pain, discomfort and difficulties with appliance adhesion that result in leakages [3]. PSH reduces health-related quality of life (HRQoL) and causes limitations in sexual function, travel, social interaction and return to work [4]. Patients with PSH may also present with bowel obstruction and strangulation that necessitates emergency surgery, which carries a substantial morbidity and mortality [5]. The 2014 Association of Coloproctology of Great Britain and Ireland (ACPGBI) Delphi exercise identified the prevention and treatment of PSH as the second most important noncancer-related research question [6]; surgeons in North America similarly regard these issues as research priorities [7]. Surveys of patients with stomas have also highlighted the importance of research into PSH risk from their perspective [8].

The incidence of PSH varies widely in the literature, with rates up to 94%, and depends upon definition, mode of diagnosis (self-reported, clinical examination, radiological), type of stoma and duration of follow-up [9,10]. The true incidence of PSH, however, is unknown due to a lack of high-quality prospective data about current surgical practice. Despite the large number of patients undergoing stoma formation each year, there is limited high-quality evidence about strategies to prevent PSH. Factors related to both the patient and surgical technique have been proposed to be important in influencing the risk of PSH development. Patient factors are often not amenable to modification due to the need for timely surgery, especially in patients with cancer. Surgical technical factors are potentially modifiable and include the site, size and shape of the stoma trephine in the musculofascial layers of the abdominal wall, routing of the afferent stomal limb and whether mesh is used as a prophylactic reinforcement [11,12]. However, the way in which surgeons create a stoma varies widely and the relative influence of technical compared with patient factors on the risk of development of PSH is unknown.

The UK cohort study to investigate the prevention of parastomal hernia (the CIPHER study) aims to describe the incidence of symptomatic and radiologically confirmed PSH during at least 2 years' follow-up. CIPHER also aims to evaluate the effects of key technical surgical steps during index stoma formation on the risk of subsequent PSH formation.

METHOD

Study design

The CIPHER study is a multicentre, prospective cohort study that is informed by preliminary work to develop symptom measures and methods detailing the technical aspects of stoma formation.

The objectives of the study are as follows:

1. To describe the incidence of PSH formation within 2 years of formation of all types of stoma.
2. To describe the risk of PSH for (i) different types of stoma formed (e.g. colostomy versus ileostomy and end versus loop) and (ii) different surgical techniques used to create the stoma.
3. To estimate the cost-effectiveness of commonly used types of mesh prophylaxis (e.g. biological, synthetic) versus no prophylactic mesh in prevention of PSH and improving health-related quality of life.

Setting

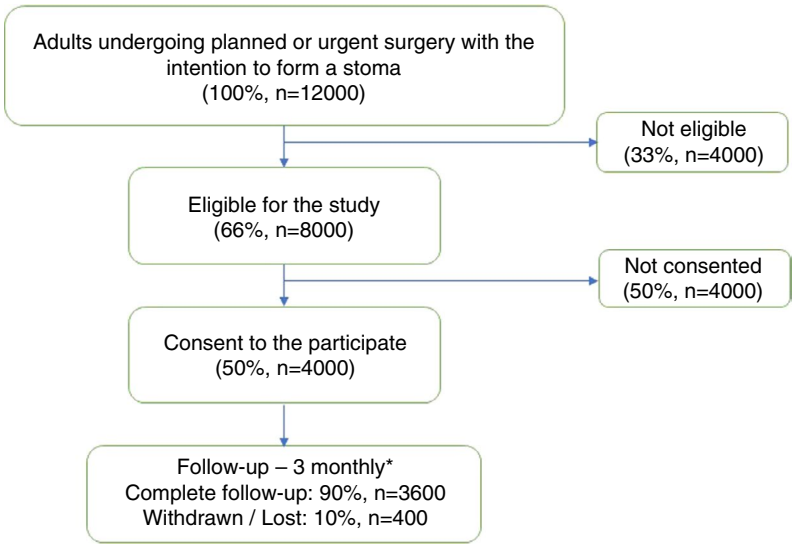
A minimum of 80 acute NHS trusts across the United Kingdom will recruit participants. The recruitment target is 4000 participants (Figure 1).

Study population

The target population is adults (≥18 years) undergoing elective or expedited surgery using the NCEPOD classification of intervention (https://www.ncepod.org.uk/classification.html) with the intention to form a stoma, irrespective of the primary indication for the planned surgery (e.g. colorectal cancer, inflammatory bowel disease etc).

Patients will be excluded if they are undergoing emergency surgery, have had a previous abdominal wall stoma or are having surgery with the intention of forming a double-barrelled stoma or urostomy. Patient must have a life expectancy of more than 12 months from the time of their procedure.

Loop ileostomies were originally excluded because we expected a large proportion to be closed quite quickly, reducing their time 'at risk' of PSH. We decided to include loop ileostomies when we became aware that a significant proportion were never being closed (25%–30%) [13] and that the median time to closure for patients who had undergone anterior resection was 9 months [14]. This population is not inherently different from the population



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

FIGURE 1 The study schema for CIPHER

having a permanent stoma formed and, against a postulated PSH rate of 40% at 2 years, has an important burden of disease. The COVID-19 pandemic has, regrettably, lengthened the time to close for many participants and this group will now contribute more time at risk.

Interventions

The study interventions are the different surgical methods of stoma formation. We undertook a preliminary study to define the key surgical steps of interest in stoma formation (elsewhere described as Phase A, with this cohort study being Phase B) [15]. This involved nonparticipant observation in the operating theatre, interviews with gastrointestinal surgeons and stoma nurses and video recordings of stoma formation surgeries [16]. The surgical steps of interest that were identified include:

1. the method of forming the stoma trephine
2. the use of mesh to reinforce the stoma trephine
3. the use of the stoma trephine as a specimen extraction site
4. closure of other wounds formed during the procedure
5. spouting of the stoma lumen.

Primary outcome

The primary outcome of the study will be the incidence of PSH after stoma formation surgery (minimum 2 years' follow-up). To meet the definition of a PSH for this study, participants must have both symptoms of a PSH as evidenced by a custom Stoma Questionnaire (see below, and Appendix S1 in the Supporting Information) and an anatomical PSH, as evidenced by independent assessments of CT imaging (see below and assessment items in Appendix S1).

Participants are asked to describe their PSH symptoms using a custom-designed stoma questionnaire developed in the preliminary study [15,17]. CT scans carried out in the course of a patient's usual NHS care are being assessed for all participants, with anatomical PSH being graded using the EHS classification (EHS class I, II, III or IV [18]). CT scans taken up to 6 months before or 3 months after completion of the stoma questionnaire are valid for assessing anatomical PSH. CT assessors will collect additional details from CT scans (e.g. linear measurement in axial and craniocaudal planes of the stoma trephine defect rather than the dichotomous classifications of size >5 cm versus ≤5 cm), including measurement of the size of the PSH sac. The EHS criteria for classifying PSH as small or large will be reviewed on the basis of these additional data as the study progresses.

Secondary outcomes

The secondary endpoints will include number of days spent in hospital and on the intensive care unit (ICU) during admission for index surgery, postoperative complications, quality adjusted life years (QALYs) and survival. We will also estimate the cost of hospital care during follow-up and primary care, health and social care resource use and societal costs associated with stoma.

Sample size

The study aims to recruit 4000 participants over a 24-month period and to follow all participants until the last recruited participants have been followed for a minimum of 24 months. Table 1 shows the hazard ratios that a study of this size will be able to detect at the 5%

TABLE 1 Hazard ratios detectable in the CIPHER study for a range of assumptions, based on a cohort of 4000 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

Abbreviation: PSH, parastomal hernia.

level (two-sided) under different scenarios given the uncertainty in the incidence of PSH (we have considered incidences of 30% and 40% as plausible) and the varying frequencies with which the surgical methods of interest are used (we have assumed ratios of 1:1, 1:2, 1:5, 1:10 and 1:20 when comparing one surgical technique with another). The correlation of a particular surgical method with other covariates is also unknown and we also considered the impact of a range of correlations (0, 0.3 and 0.5). For simplicity, we have assumed a binary exposure variable (i.e. yes/no to a particular surgical method). The target sample size assumes an attrition rate of 10% at 2 years after index surgery. In practice, the power of the study will be increased by a follow-up longer than 2 years for a proportion of participants and decreased by a follow-up shorter than 2 years for a proportion (e.g. due to mortality, participants requesting to withdraw or planned closures of loop ileostomies). These factors are being monitored as data accrue for the study; their consequences for the target sample size will be modelled and the target sample size revised if appropriate.

Patient consent

All eligible patients are or will be given or sent a patient information leaflet (PIL) and have the opportunity to deliberate before being approached for their written informed consent. In most cases, the consent process will take place prior to the patient having surgery

to form a stoma. In some instances, consent may be taken retrospectively following the patient's surgery. When this happens, patients 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. Patients also have the option of consenting to either or both of the following: for their data to be used in future ethically approved research and for their contact details to be passed on to other researchers.

Data collection

Data will be collected at baseline, intraoperatively, at discharge and at 6 weeks and 6, 12, 18 and 24 months after surgery. Participants can choose to continue to be followed up at 6 monthly intervals after 24 months until the end of the study.

The study will be run by the managing trials unit in the same way as it manages randomized trials. The study has a custom-designed database, with validation of date fields, into which sites enter data. The database interrogates the data and reports queries to sites, that sites have to address. The number of data queries at sites are reviewed regularly by the central study team and nominated individuals at sites contacted if the queries are not being addressed. The managing trials unit periodically reviews reports of the accruing data, and the sponsor is able to review study conduct by the trials unit.

Patient-completed questionnaires

The questionnaires will include HRQoL questionnaires [EQ-5D-5L (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/) and SF-12 (https://www.rand.org/health-care/surveys_tools/mos/12-item-short-form.html)], a wound questionnaire [19], a questionnaire about stoma symptoms and a questionnaire about how patients are coping with the change to their life (Brief COPE questionnaire [20]). The stoma questionnaire is a purpose-designed questionnaire about stoma symptoms developed specifically for this study (see Appendix S1) [17]. The questionnaire was developed from interviews and previous literature and focused, through piloting, on questions that elicited more extreme responses in patients known to have a PSH. Setting a threshold to define symptomatic was not possible based on the sample of patients available for developing the instrument. This process is in progress using data from questionnaires completed during the study.

Each questionnaire will be completed at the timepoints outlined in Table 2.

TABLE 2 Timing of collection of data items

	Time of data collection with respect to date of index surgery						
	Before	During	Up to discharge	6 weeks after	6 months after	12 months after	6-monthly to study end
Screening log	✓						
Consent form	✓						
Participant baseline details	✓						
Surgical details		✓					
Complications			✓				
Index hospitalization resource use		✓	✓				
Stoma care nurse contacts with participants and hospital admissions				✓	✓	✓	✓
Exercise, support garment data				✓	✓	✓	
EQ−5D−5L, SF−12	✓			✓	✓	✓	✓
Wound questionnaire			✓	✓			
Community-based health care					✓	✓	✓
Stoma questionnaire					✓	✓	✓
Brief COPE questionnaire						✓	
Request CT scans, taken as part of patient's usual care				✓	✓	✓	✓

Note:: Inpatient and outpatient hospital episodes will be extracted from Hospital Episode Statistics data, which will be requested periodically throughout the study.

CT scans

CT scan images performed as part of the participants' routine clinical care, at baseline (up to 3 months prior to their stoma surgery) and during the period they are in the study will be obtained through the image exchange portal (IEP), an image sharing system run by SECTRA (https://medical.sectra.com/product/sectra-image-exchange-portal/). These images will be assessed by surgical trainees using the EHS classification system [2]. CT scan grading by trainees will be carried out in duplicate, using a web application developed for the study. CT scans will be viewed through the IEP. EHS classifications that differ by two or more EHS grades will be adjudicated by an expert.

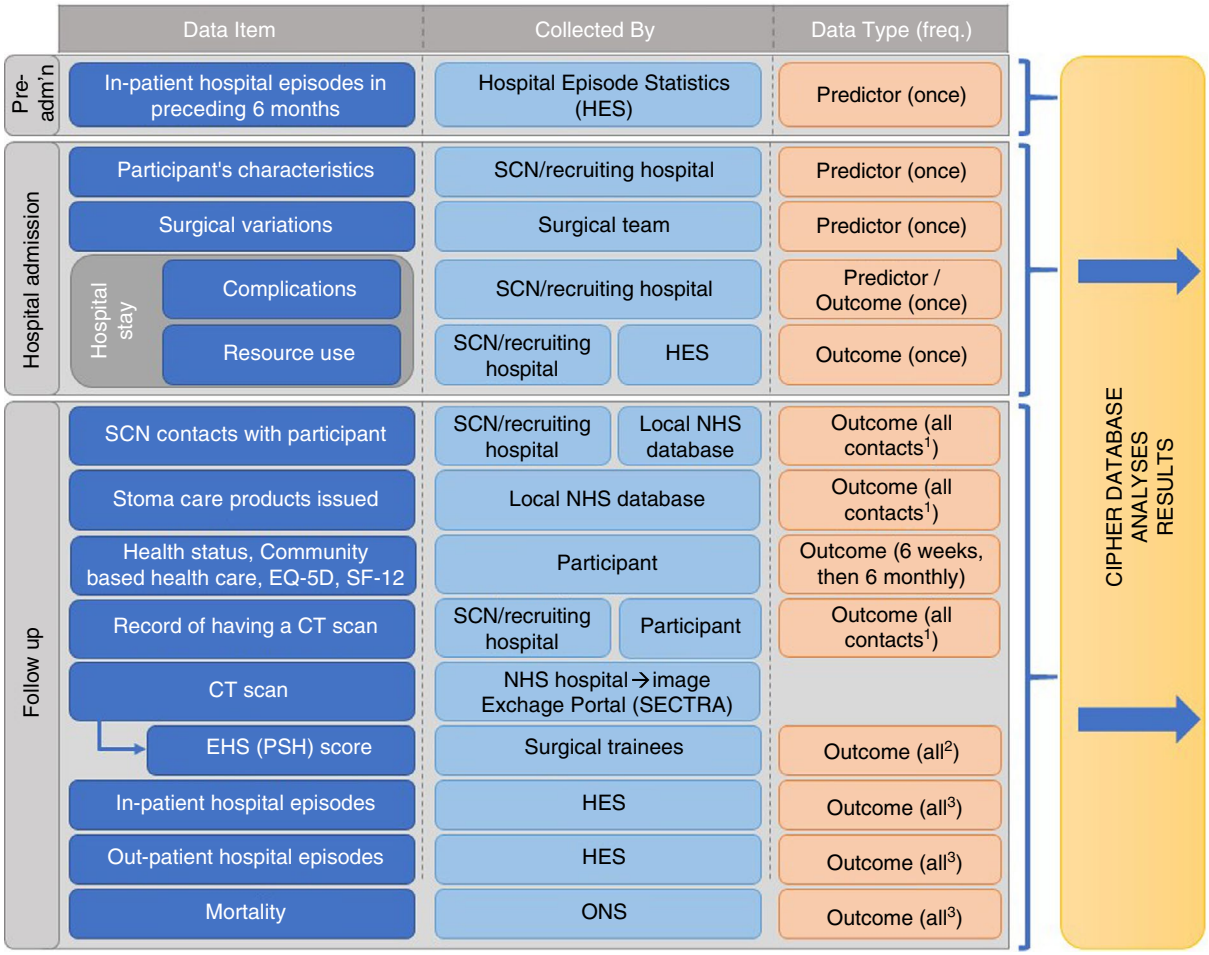
Routine data sources

Information about hospital admissions, outpatient hospital appointments and participants who die during the study will be obtained from national datasets [i.e. from NHS Digital, Information Services Division (ISD) Scotland and Patient Episode Database for Wales (PEDW)]. Information about resource use will be collected from participants directly and from routinely collected data sources, for example NHS Digital (hospital episode statistics) and databases used locally to record stoma care nurse (SCN) visits and stoma care products issued (e.g. the MiME database). The data will be collected by different people, as outlined in Figure 2.

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 postoperative inpatient stay and (iii) stoma care



Footnotes:

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

FIGURE 2 Data collection diagram (EHS, European Hernia Society; NHS, National Health Service; ONS, Office for National Statistics; PSH, parastomal hernia; SCN, stoma care nurse)

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 QALYs estimated using the EuroQol EQ-5D 5L. We will conduct a model-based cost-effectiveness analysis comparing synthetic mesh, biological 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 randomized controlled trials with longer follow-up to estimate the relative risks of incidence of PSH with mesh (synthetic or biological) 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 [21]. Full details of the cost-effectiveness model will be provided in a health economics analysis plan.

Statistical 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. The primary outcome, time to PSH 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 (i.e. different surgical methods) 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 [22]. 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 they 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.

Risk of bias

We have designed the study to minimize the risk of bias, based on bias domains identified as relevant to nonrandomized studies of interventions [22]. All patients undergoing stoma formation surgery are being screened for the study and the same eligibility criteria are being applied without selection. We expect that the patients recruited to the CIPHER study will be generalizable to the wider population, since about half of UK colorectal units have or are recruiting participants, and recruitment is constrained only by sites having the time to approach patients and patients' willingness to take part. If we find that surgeons are using specific surgical techniques based on patients' baseline characteristics, we will control for this by conventional and multivariable methods. The key surgical steps have been carefully defined and parameters have been applied to the electronic case report form to avoid any bias in measurement of the interventions. The risk of missing data has been minimized by using multiple methods to collect the data needed for the study, especially data relating to the follow-up of participants (e.g. from the patient and the study team).

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, and it is unlikely that they have expectations about the potential influence of variations in surgical methods on outcome. Research personnel collecting outcomes in hospital or during follow-up after discharge do not know the surgical methods used; similarly, 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. The exception is the use of mesh: patients are likely to be informed when this is used, and assessors may (depending upon type of mesh used) be able to see this on the CT scans.

Study organization, administration and governance

The CIPHER study is funded by the NIHR Health Technology Assessment (HTA) Programme (grant ref. 14/166/01). The development work for the questionnaire and methods for understanding surgical techniques were funded by the MRC Hub for Trials Methodology Research in Bristol (ConDuCT-II Hub). The study sponsor is the Royal Devon and Exeter NHS Foundation Trust and the study is managed by the Clinical Trials and Evaluation Unit, Bristol Trials Centre, Bristol. The CIPHER study is overseen by an independent study steering committee. The study has been designed with input from public and patient groups who fed back comments on the study protocol and reviewed patient-facing documentation. The study is supported by Colostomy UK and the Ileostomy Association. The study is conducted in compliance with General Data Protection Regulations and Good Clinical Practice.

Ethical approval

This study has been reviewed and given favourable opinion by the West Midlands – Black Country Research Ethics Committee on 8 November 2017 (REC ref. 17/WM/0401). Recruitment started in January 2018.

Changes to the study protocol

In December 2018 an amendment was approved by the Research Ethics Committee to include loop ileostomies (previously an exclusion criteria) and allow retrospective consent. The amendment was implemented at sites in January 2019. The current version of the protocol is version 2.0 dated 7 November 2018.

Dissemination and data sharing

Results of the study will be submitted for publication in peer-reviewed journals. All publications relating to the results of CIPHER will use a corporate authorship, 'The CIPHER Study Investigators' with named writing committee members.

Individuals may make formal requests for data to be use in ethically approved research. Ethical approval has also been granted for the contact details of CIPHER participants who agree to be passed on to other researchers.

DISCUSSION

The way that surgeons are trained to create a stoma has not changed in over 60 years, and the impact of the technical steps during surgery on the risk of development of PSH has been poorly studied in the past. Given the frequency of stoma creation, its diverse range of indications and the severity of the sequelae of a PSH, this is somewhat surprising. As the surgical community has realized the challenge of PSH repair, characterized by high rates of complications, recurrence and lack of evidence of improvement in HRQoL, the focus has inevitably shifted towards prevention of development of PSH by investigating the techniques used at index stoma formation.

The most studied technique with more than ten randomised trials has been the use of prophylactic mesh placed at the time of stoma formation. Whilst advocated by some [2], others, including ACPGBI, Cochrane and NICE, have been more circumspect with regard to their recommendation for routine adoption [6,23,24]. This caution has been driven by two factors – first the methodological limitations of the studies on prophylactic mesh and second the lack of long-term data relating to the safety of mesh placed immediately adjacent to the bowel. The rare but significant risks of mesh erosion, fistulation and infection coupled with complex surgery to correct such problems has led many surgeons not to follow the recommendations for adoption into routine clinical practice made by some learned societies. The focus on research into prophylactic mesh represents the desire for a simple solution to a complex problem. Without knowing the optimal stoma formation technique to prevent PSH, there is a real risk that the effect of prophylactic mesh is magnified due to surgeons forming the stoma differently (i.e. in a more optimal manner) when using mesh.

The CIPHER study aims to investigate the key technical steps at index stoma surgery as well as the patient factors that are associated with formation of a PSH. It has innovatively developed specific tools to study components of surgery during stoma formation. Data therefore can be captured perioperatively to understand how techniques influence outcome. No study has so far investigated the risk factors in such detail. In addition, it has developed tools to capture patients' perspectives and symptoms. The findings of the CIPHER study should enable us to identify targets for future research in comparative randomized trials and perhaps to target such research questions to certain patient groups at highest risk of developing PSH.

CONFLICT OF INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

HT: preparation and drafting of study protocol, first draft and writing of manuscript. JMB, NB, MC, IRD, AM and TDP: study concept and design, review of study protocol, review of manuscript. AG: study design, review of study protocol, review of manuscript. WH: study concept and design, review of study protocol, health economic analysis plan and analyses, review of manuscript. CM: review of study protocol, review of manuscript. CAR: study design, preparation and drafting of study protocol, sample size and statistical analysis plan, review of manuscript. NS and BCR: study concept and design, preparation and review of study protocol, review of manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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