UK Cohort study to Investigate the prevention of Parastomal HERnia (CIPHER)

Phase A Protocol: Understanding surgery and current practice in stoma formation and developing Patient Reported Outcome Measures for Parastomal Hernia to inform Phase B of CIPHER

Version 2.0, 19th April 2016
HTA No: 14/166/01
IRAS No: 201605

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This study is funded by the NIHR Health Technology Assessment Programme (Ref 14/166/01). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Glossary / abbreviations

ACPGBI	*Association of Colo-Proctology of Great Britain and Ireland (ACPGBI)*
MRC ConDuCT-II Hub	*Medical Research Council Hub for Trials Methodology Research Collaboration and innovation in Difficult and Complex randomised controlled Trials In Invasive Interventions*
CRF	*Case Report Forms*
CT	*Computed Tomography*
CTEU	*Clinical Trials and Evaluation Unit*
HTA	*Health Research Authority*
MRC	*Medical Research Council*
NIHR	*National Institute for Health Research*
NHS	*National Health Service*
PIL	*Patient Information Leaflet*
PROM	*Patient Reported Outcome Measure*
PSH	*Parastomal Hernia*
REC	*Research Ethics Committee*
RD&E	*Royal Devon and Exeter NHS Foundation Trust*
RCT	*Randomised Controlled Trial*
SSCM	*School of Social and Community Medicine*
UH Bristol	*University Hospitals Bristol NHS Foundation Trust*
UoB	*University of Bristol*

1. Study Summary (plain language summary)

During abdominal surgery it is sometimes necessary to form a stoma (ileostomy, colostomy), with approximately 20,000 created annually in the UK [1]. Having a stoma means that a section of bowel is passed through the abdominal wall. The bowel can then empty its contents (stool/faeces) into a bag worn externally. A complication of stoma formation is the development of a Parastomal Hernia (PSH), which may occur in up to 40% of patients. A PSH is a swelling next to the stoma whereby abdominal contents protrude underneath the skin. It may cause pain and/or difficulties with stoma bag fixation leading to leakage of bowel contents and skin irritation [2]. Anxiety and embarrassment associated with PSH can influence sexual function, social interaction and work [3]. Hospital admission may be required if a section of bowel is trapped in the PSH, causing serious complications such as strangulation, obstruction or perforation that might cause irreversible damage to the bowel. Whilst some PSH may not require treatment, it is thought that at least half of all PSH lead to problems. If treatment is required, this usually involves further surgery which can be difficult and does not guarantee success. Prevention of PSH is therefore a priority.

The National Institute for Health Research (NIHR) has funded a cohort study to investigate the prevention of PSH (The CIPHER Study). The CIPHER study is in two parts. The first part (this application, Phase A) is essential to inform the second part (a separate application, Phase B). Phase A will firstly involve interview and observation work to understand the key components of how stomas are formed in the operating theatre. Researchers will observe how stomas are created by a variety of surgeons in theatre, followed by interviews with the operating surgeon. This will enable a detailed understanding of stoma formation in order to identify the surgical steps that might be important in the prevention of a PSH. Secondly, work from Phase A will develop and modify questionnaires that patients will complete in order to elicit symptoms associated with PSH, so that these can be accurately assessed in Phase B. Researchers will interview patients to ask for their views on problems of living with a PSH. They will also discuss existing questionnaires with patients to help find out if they include questions that address all the potential problems associated with a PSH. Both outputs will be tested and used in the main study (Phase B).

This study will be conducted by a highly experienced team at the University of Bristol School of Social and Community Medicine (SSCM). It will be performed in conjunction with surgeons at several hospitals in the UK and a registered clinical trials unit (the Clinical Trials and Evaluation Unit, Bristol).

2. Background

In the UK approximately 20,000 new stomas are created annually [1]. Within two years of the initial stoma formation, up to 40% of patients may have developed a PSH. This means that there is a swelling next to the stoma whereby abdominal contents protrude underneath the skin. While some PSHs are asymptomatic, it is thought that at least 50% are associated with problems. The most common symptoms are pain (35%) and difficulty attaching the stoma appliance (28%) [3]. This may result in the leakage of bowel contents (28%), which can cause skin irritation, anxiety and embarrassment [3]. Some patients require emergency

admission to hospital due to bowel obstruction, strangulation or perforation. This may necessitate surgery, potentially including revision of the stoma, which can be associated with the development of further PSH. Prevention of PSH is therefore a priority. Indeed this was recently supported by a Delphi survey of the Association of Coloproctology of Great Britain and Ireland (ACPGBI), who ranked optimisation of methods to prevent and repair PSH as a key research question [4].

The NIHR has funded the UK Cohort study to Investigate the prevention of Parastomal Hernia (CIPHER). CIPHER is designed with two parts (Phase A and B). Phase A involves essential preliminary work before the cohort study can take place (Phase B). Phase A will identify the data that should be collected in order to investigate the prevention of PSH. This includes information about surgical technique (Part 1) and development of a patient-reported outcome measure (Part 2).

Both patient and surgical factors may influence the risk of developing PSH. Patient factors include advanced age, obesity, wound infection, malignancy, inflammatory bowel disease, immunosuppression and a raised intra-abdominal pressure [5-7]. Surgical risk factors are less well defined. Risks are considered to relate to the methods of stoma formation. There are multiple techniques used in practice with no overall standard approach. For example, location and size of the abdominal wall defect created during stoma formation is thought to vary between surgeons [6]. Some surgeons use mesh around a stoma to help prevent PSH, whilst others do not [8]. Additional factors that may influence PSH formation are whether the surgery was planned or unplanned [6] and the seniority of the surgeon performing the procedure. Part 1 of Phase A of the CIPHER study will investigate variations in surgical methods and identify key surgical steps that may influence PSH formation. This will involve reviewing the current literature and producing descriptive case studies of stoma formation in the operating theatre. These steps will thus define the surgical variables of interest for measurement in the cohort study (Phase B).

A further problem is the lack of standardised methods to assess and diagnose PSH. While diagnostic criteria and classifications of PSH severity are available, they vary and are not consistently used [9-11]. Existing studies used a variety of diagnostic methods including intraoperative findings, clinical diagnosis [12-14] and computerised tomography (CT), each of which has limitations in terms of interpreting results. Clinical examination alone may be insufficient to detect a small (but nevertheless symptomatic) PSH. Using intraoperative findings cannot be justified as a diagnostic tool alone because not all PSH will require surgery and many may, therefore, be missed. Finally, although CT is highly accurate at identifying PSH, it cannot distinguish between symptomatic and asymptomatic PSH, or those which do or do not require repair. Moreover, its routine use to follow up all patients may not be justified because of National Health Service (NHS) costs and radiation exposure. One way of improving the diagnosis of PSH, would be to initially use patient reported outcome measures (PROMs) to determine and classify symptoms. CT imaging could then be used to establish the diagnosis. However, there are currently no PROMs specific to PSH. Part 2 of Phase A will involve developing and testing PROMs for PSH. This will enable the identification of patients experiencing threshold levels of symptoms that would warrant further investigation to diagnose a symptomatic PSH.

This research is sponsored by the University of Bristol. Phase A will be managed by members of the MRC ConDuCT-II Hub for Trials Methodology Research working with the surgeons in CIPHER and Clinical Trials and Evaluation Unit (CTEU Bristol).

3. Aims and objectives

The overall aim of Phase A is to undertake feasibility work to inform the design of Phase B.

Specific objectives are:

- Part 1: To identify the surgical steps and other factors relevant to PSH development that will be used in CIPHER Phase B (Section 4)

- Part 2: To develop a Patient Reported Outcome Measure to use in Phase B to identify symptomatic PSH (Section 5)

4. Part 1: Identification of surgical steps and other surgical factors relevant for PSH formation

4.1 Study Methods

This study will be a mixed methods modification of a realist evaluation. Realist process evaluation is an increasingly popular method of researching complex interventions and has previously been used in surgical research [15].

4.1.1 Literature review

A literature review will be undertaken to identify studies describing techniques of stoma formation. Key steps and variations will be summarised and will inform the development of theories about how different surgical techniques might influence the development of PSH.

4.1.2 Case studies

Descriptive case studies of stoma formation in the operating theatre will be undertaken using previously tested methodology [16]. Each case study will comprise of; i) digital video data capture; ii) non-participant observation of operations in which stomas are formed; and iii) interviews with surgeons and specialist stoma nurses. Data capture and non-participant observation of stoma formation will occur at the same time.

4.1.2.1 Digital video data capture of stoma formation

Stoma formation will be captured using an approved digital video camera (according to the research protocols and in line with local Trust guidelines). The digital video capture will start when the steps of stoma formation begins and will stop upon completion. Digital video capture will focus on the abdomen alone, concentrating on the surgical steps of stoma

formation only. Images of the professional or patient participants will not be identifiable. Audio data will not be captured.

4.1.2.2 Non-participant observation

Non-participant observation will be performed by two surgical trainees (NB and CM) who are members of the research team. The surgical trainees will take field notes of the stoma formation, documenting the instruments and movements used. Communication (verbal and non-verbal) and context of relevance to the operative strategy will also be documented.

4.1.2.3 Semi-structured Interviews

Brief interviews will be undertaken with surgeons after stoma formation is complete. These interviews will be guided by a topic guide (Appendix I) that will be adapted by what researchers observe in theatre. The interviews will be audio recorded and are expected to last between 30-45 minutes. The interviews will explore the surgeons' rationales for surgical method used, (including (un)planned variations according to patient, clinical and procedure-related factors) and identify reasons for any unusual events or deviations from the usual procedure. These interviews will occur as soon after the operation as possible (ideally in the operating theatre at the end of the procedure) but may occur at a later time at a place convenient to the professional participant. Audio recordings will be made using an approved encrypted device. Any identifiable data in the recordings will be anonymised.

Further interviews may be undertaken with surgeons and stoma nurse participants at a later date. During these interviews, theories developed from the case studies and literature review will be presented to the clinicians to further explore their perceptions. The interviews (which are expected to last between 30-45 minutes) will occur at a time and place convenient for the professional participant and may occur in person or over the telephone. This data will be audio recorded using an approved encrypted device. Any identifiable data in the recordings will be anonymised.

4.2 Study population

4.2.1 Inclusion and exclusion criteria

For this methodological work the intention is that the study population is as inclusive as possible and reflects those patients eligible for Phase B of the study. To this end, patients aged 18 years or over requiring formation of an ileostomy or colostomy will be approached. Excluded will be those patients in whom the surgeon intends to form a loop ileostomy, double-barrelled stoma, or urostomy. Patients who have had a previous abdominal wall stoma and those with a life expectancy of less than 12 months will also be excluded.

Surgeons to be studied include consultants and surgical trainees of all grades involved in operations in which abdominal stomata are formed. Stoma nurses from participating sites will also be interviewed.

4.2.2 Target sample

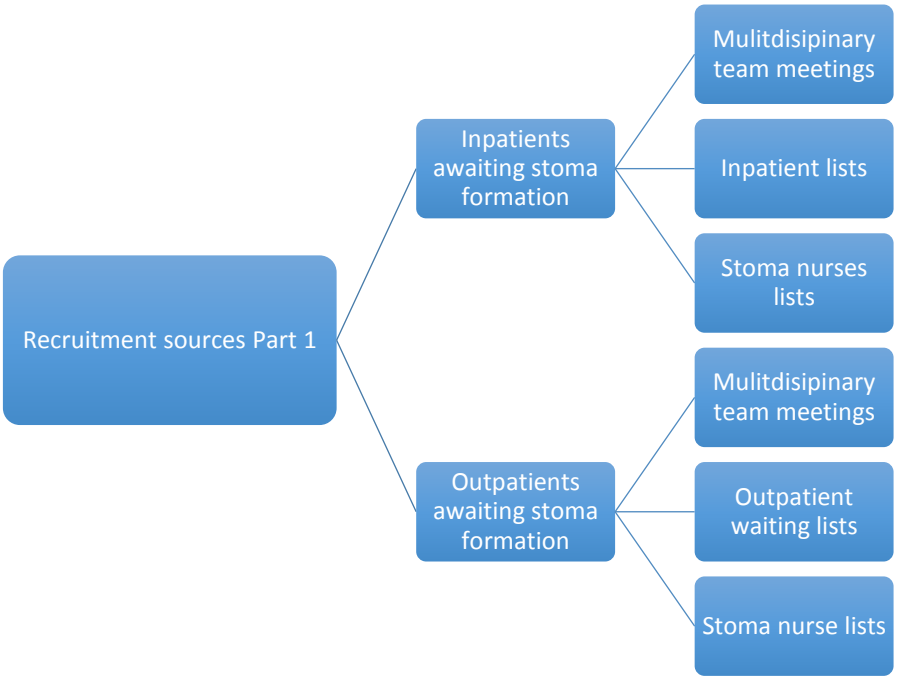
Approximately 20 patients are expected to be required and approximately 20 surgeons and stoma nurses. A maximum variation will be obtained, representing the widest possible range of stoma types meeting the inclusion criteria (above). This will include planned and unplanned operations, ileostomy and colostomy formation, and observing procedures undertaken by colorectal specialists as well as general surgeons. If saturation of data is not achieved we will consider recruiting alternative sites.

4.3 Recruitment and consent

Eligible inpatients and outpatients will be identified by surgical teams, research and stoma nurses at participating centres through multi-disciplinary team meetings, inpatient lists, outpatient clinics, stoma nurses' lists. Patients will be screened for eligibility through review of their medical notes. Those considered eligible and interested in participating will be given written information (patient information leaflet (PIL) 1 V2.0 19th April 2016). A member of the research team will fully explain the study to the patient. Outpatients may be given written and verbal information at clinic attendance, pre-assessment (ideally) or when they attend on the day of surgery (not ideal). Participants who agree to take part will be asked to sign a consent form a minimum of five hours after receiving written and verbal information about the study, although it may be much longer if information is sent by post before planned surgery.

We will try as hard as possible to include participants who do not understand English fully by liaising with an interpreter if available. However, our ability to do this will be determined by the day−to−day availability of this service.

Surgeons and stoma nurses eligible for participation will be identified by members of the research team. Professional participants will be given written study information in person and/or by email (PIL 2 V2.0 19th April 2016 for surgeons and PIL 6 V1.0 19th April 2016 for stoma nurses), usually several weeks in advance (e.g. for planned operations) or at least two hours in advance (e.g. unplanned operations) to allow for time to consider participation. Consent for the case study (including video data collection, observation and interviews) will be taken collectively by the research team. Stoma nurses will be asked to consent to the interviews alone.



4.4 Data collection

The following data will be collected:

(a) Baseline information about patients (for example: age, sex, co-morbidities), the operation (for example: planned or unplanned, name, duration, timing) and surgeons (for example: age, sex, number of years of training, sub-specialty) will be collected prior to surgery. Baseline details will also be collected about Stoma Nurses (for example: age, sex and number of years of training)

(b) Digital video data capture of surgical stoma formation, focusing on the abdomen only

(e) Non-participant field notes of surgical stoma formation

(e) Audio recordings of interviews

4.5 Analysis

Data collection and analysis will run in parallel. Analysis will be performed by the researchers (NB and CM) and overseen by the qualitative research team at SSCM (LR). Digital video capture will be viewed, unedited and transcribed from beginning to end. Transcription will include the documentation of movements, instruments and actions visible on the screen. These will be grouped into operative steps and components, creating a stepwise account of each procedure. This process will be guided by an existing typology of surgical interventions [17]. Field notes of non-participant observations will be transcribed and aligned with the corresponding video transcripts, to allow simultaneous analysis. Audio recordings of interviews will be transcribed verbatim from beginning to end and used to supplement the data from the case studies. Information gained will be used to expand on the theories about

surgical risk factors for PSH, adding to/supplementing those identified from the literature review.

The findings will be discussed within a meeting with study investigators and participating surgeons. The attendees will agree on the key surgical steps in stoma formation that will then be collected as part of the CIPHER cohort study (Phase B).

4.6 Risks and anticipated benefits

We foresee no risks to the patient during non-participant observation. Patients participating will have a letter (Letter 3: GP notification case studies V1.0 19th April 2016) sent to their regular GP's to notify them of their study involvement (Appendix VI).

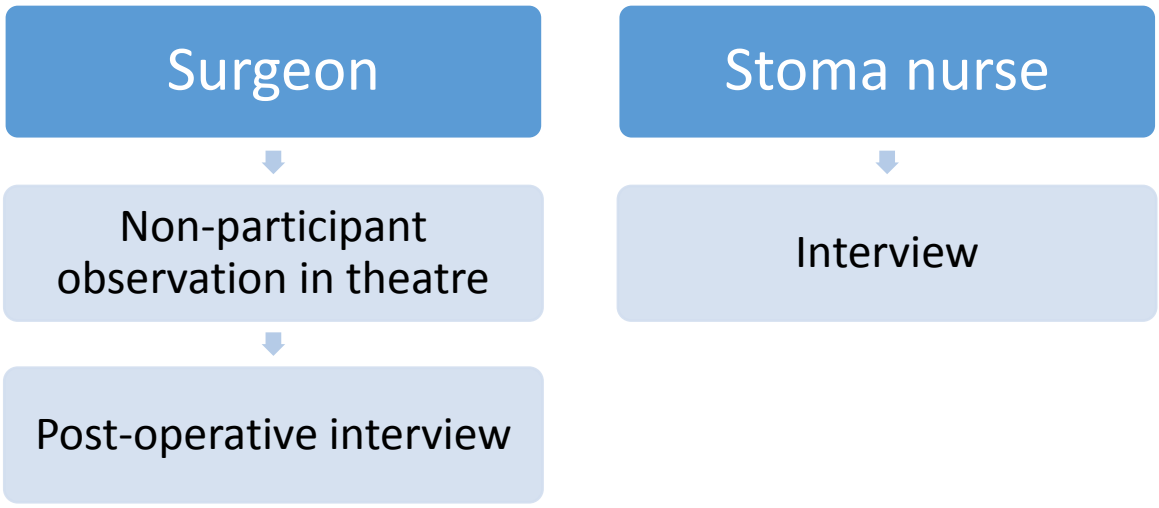
The presence of two extra individuals in theatre may present a slight burden to the operating surgeon. This can be minimised by utilising surgical trainees as non-participant observers, as they will be familiar with the environment and mindful of their presence in theatre. The only disadvantage to surgeon participants is the time cost of participating in interviews. Benefits for surgeons include the opportunity to participate in shaping the data collection for the cohort study and future RCT. Moreover, they may enjoy and learn from thinking about the rationale for their choice of technique.

Risks to the research team during non-participating observation are the same as the risks to other non-participating individuals in theatre. Contact with bodily fluids and/or *"sharps"* (e.g. blades and needles) is possible, but highly unlikely. These risks will be minimised through using non-participating observers with theatre experience. Non-participating observers will adopt the same personal protection equipment as other non-participating individuals and will maintain a safe working distance in theatre.

4.7 Frequency and duration of follow up

There is no planned follow up for either patient participants or clinician participants.

FIGURE 1: Part 1 participant pathway flow chart



5. Part 2: Developing a patient reported outcome measure to detect symptomatic PSH

The aim of Part 2 of Phase A is to develop a Patient Related Outcome Measure (PROM) to identify symptoms of a PSH. Part 2 involves questionnaire surveys and cognitive interviews with patients living with and without a PSH and interviews with healthcare professionals. The measure will be used in Phase B to follow up patients who have had a stoma formed to detect the symptoms of a PSH. A diagnosis would then be established amongst those patients using CT imaging.

5.1 Methods

5.1.1 Literature review

The existing literature will be reviewed to look for PROMs relevant to PSH. Scoping work has identified several questionnaires for patients with a stomas and colorectal cancer [18, 19]. Although no PSH specific questionnaires have been identified, the relevant health domains (and items used to measure the domains) have been extracted from existing questionnaires and used to inform an item tracking matrix. The domains have also been used to form a semi-structured interview schedule (Appendix II/III). These will be used to form the basis of interviews with patients and staff to identify the symptoms and problems experienced by patients with a PSH that are different (or worse) than those experienced by patients with a stoma that is not complicated by a PSH.

5.1.2 PROM development through interviews

One-to-one semi-structured interviews with patients, surgeons, and stoma nurses will be conducted by a member of the research team. These interviews will explore symptoms and problems associated with their PSH. The questions asked will resemble those asked by a

stoma nurse. As part of the interviews patients will look at pre-existing measures identified by the literature review and asked if they are relevant and understandable. Interviews will be informed by the semi-structured interview schedule (Appendix II/III) and will take place at a time and place convenient to participants (in the hospital or at their home), using a room, venue or setting which is suitably quiet and private. Interviews are estimated to last 20-40 minutes. We expect to interview approximately 10 patients. Interviews will continue until saturation is reached, which means the point at which no new ideas or theories emerge from the data collected. Interviews will be digitally audio-recorded with the consent of participants and supplemented with field notes made by the interviewer. All recorded data taken during and after the interviews will be transcribed verbatim.

A thematic analysis will be undertaken to identify key symptoms and health domains relevant to PSH and that might distinguish the symptoms from having a stoma alone. The interview data will supplement the item tracking matrix which will lead to new item development or modification. A selection of pre-existing items and synthesis of new items will together inform the new measure using standard questionnaire development methods that will produce a measure ready for pre-testing.

5.1.3 Pre-testing the PROM questionnaire

Once the PROM is developed it will be pre-tested by a different sample of patients to establish its face validity and acceptability. These participants will undergo a cognitive interview and be asked to complete the questionnaire as well as comment on their understanding of each item. Interviews will be guided by cognitive probes e.g. 'What does this symptom mean to you?' and 'Are there other words you would use to describe it?'. Problematic items (e.g. confusing or difficult to answer) will be documented and discussed in more depth after completion of the tool/questionnaire. The wording, format and rating scale for possible items will be discussed and suggested improvements or alternatives to those used in existing measures will be sought. Cognitive interviews and data analysis will be carried out as an iterative process and used to modify and reword items in the questionnaire to improve understanding. Further pre-testing with patients will be undertaken until this is achieved. The interviews will occur at a time and place convenient for the patient and are expected to last 30 minutes. It is expected that approximately 10 patients will be interviewed at this stage.

5.1.4 Developing traffic light levels of threshold for further investigation of symptomatic PSH

Following completion of pre-testing, the ability of the new PROM to identify symptomatic PSH will be investigated. A scoring system will be developed by asking a further sample of patients living with stomata, with and without a PSH, to independently complete the measure. Approximately 10 patients will then undergo a clinical interview and brief examination of the stoma by a medically trained clinician (who will be blinded to the results of the questionnaire). At this interview if a PSH is detected the patient will be offered a clinical appointment with their normal team to investigate and discuss it further.

Data from the questionnaires, interviews and clinical examination findings will be synthesised and used to inform the development of a scoring system. The scoring system for

the measure will have three levels of threshold (red, amber and green) to determine whether further investigation of suspected PSH is warranted. A green score (low scoring) on the questionnaire will be suggestive of no PSH or an asymptomatic PSH that does not require further investigation. An amber score (middle scoring) on the questionnaire would suggest moderate symptoms warranting further non-urgent investigation, and a red score (high scoring) would suggest alert symptoms requiring urgent investigation.

The interviews and examination will occur in a suitable location at a time convenient for the patient. This process is expected to last 20-40 minutes. The thresholds for red, amber and green defined by this process will be used during the cohort study, with the PSH symptom score being a secondary outcome measure. The scoring system will be validated during the first part of the cohort study by undertaking a cross sectional study of patients known and/not known to have a PSH hernia too.

5.2 Study population:

5.2.1 Inclusion criteria

For all these parts of the project (PROM development through interviews, pre-testing the questionnaire and developing traffic light levels of threshold for further investigation of symptomatic PSH), patients eligible for participation include: Patients over 18 years who are able to give written consent, and who have an ileostomy or colostomy in place.

5.2.2 Sample size

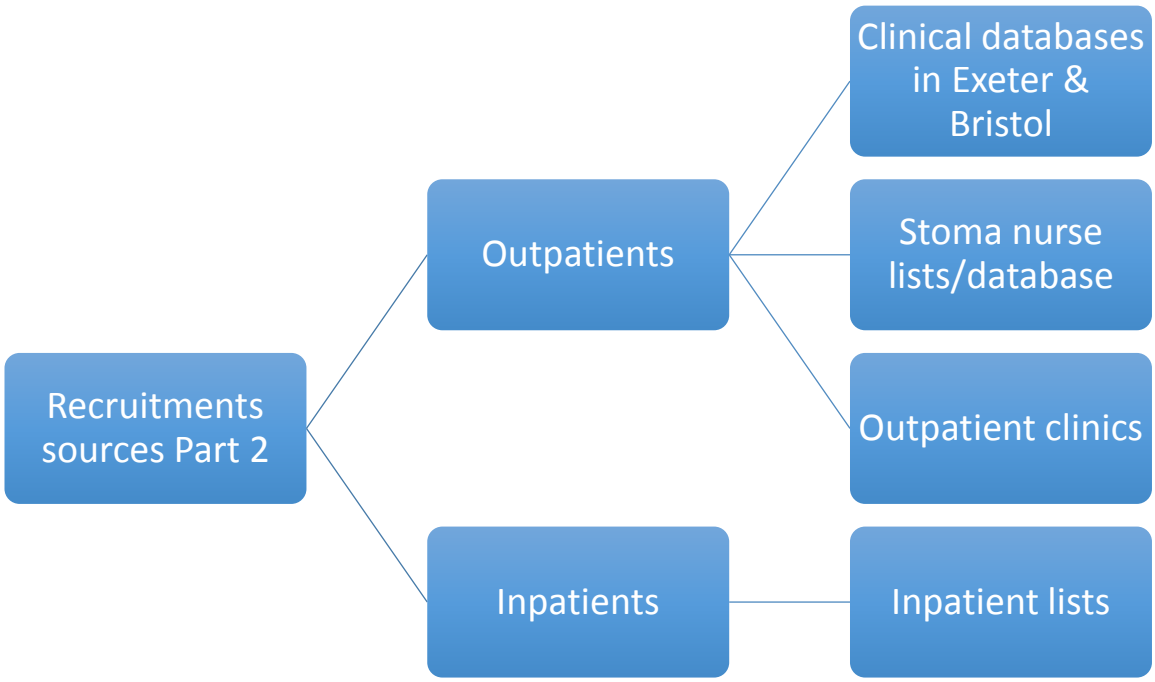
For each section of Part 2 we expect to interview a sample of 10 patients. For developing the PROM through interview (5.1.2) we expect to interview approximately 10 clinicians.

5.3 Recruitment and consent

Patients with stomata with or without a PSH will be identified from established clinical databases of patients who have stomas (maintained in Exeter and Bristol over several years), via outpatient clinics, inpatient lists and databases kept by stoma nurses. Patients will be screened for eligibility by the healthcare team through review of their medical notes and any existing cross sectional (CT) imaging. Patients will receive a letter of invitation (Patient letter 1 V2.0 19th April) and written information PIL 3 (V2.0 19th April 2016) or 5 (V2.0 19th April 2016) either by hand or post. Inpatients and outpatients will receive both the letter and PIL 3 (V2.0 19th April 2016) or 5 (V2.0 19th April 2016) followed by a member of the research team fully explaining the study to the patient. Participants who agree to take part will be asked to sign a consent form a minimum of four hours after receiving written and verbal information about the study.

We will try as hard as possible to include participants who do not understand English fully by liaising with an interpreter if available. However, our ability to do this will be determined by the day−to−day availability of this service.

Surgeons and stoma nurses eligible for participation will be identified by members of the research team. These professional participants will be given written study information in person and/or by email (PIL 4 V2.0 19th April 2016), usually several weeks in advance or at least two hours in advance to allow for time to consider participation.



5.4 Data collection

The following data sources will be collected:

5.4.1 Developing PROMs through interview

(a) Consent and baseline information from patient participants will be collected prior to any interviews taking place

(b) Record of staff who conduct interviews

(c) Audio recordings of interviews

(d) Field notes of the interviews

5.4.2 Pre-testing the PROM questionnaire

(a) Consent and baseline information from patient participants will be collected prior to any interviews taking place

(b) Record of staff who conduct interviews

(c) Field notes of the interviews

5.4.3 Developing traffic light levels of threshold for further investigation of symptomatic PSH

(a) Consent and baseline information from patient participants will be collected prior to any interviews taking place

(b) Record of staff who conduct interviews

(c) Results from PROM questionnaire

(d) Field notes of the interviews and clinical examination

5.5 Analysis

5.5.1 Developing PROMs through interview

The researcher, overseen by LR, NB and JMB, will perform a content analysis of the semi-structured interview data. A list of themes will be tabulated using a framework approach and crosschecked against the items and health domains derived from pre-existing measures identified in the literature search. Interviews and analyses will be performed as iterative processes so that emerging themes can be included as topics for discussion in subsequent interviews.

5.5.2 Pre-testing the PROM questionnaire

This will be qualitative and iterative. Changes will be made following discussion by the research team. The item tracking matrix will be maintained as a document to demonstrate rationale and changes to the questionnaire as it develops.

5.5.3 Developing traffic light levels of threshold for further investigation of symptomatic PSH

The data analysis from the questionnaire as well as interview and examination will occur at the SSCM and be performed by members of the research team. Data from the questionnaire and findings from the clinician interview and examination will be used to inform the development of the traffic light scoring system.

5.6 Risks and anticipated benefits

Participants in Part 2 may gain a greater understanding of their stoma and may benefit from having an opportunity to discuss any problems or concerns regarding their stoma. It is possible that patients may be upset by being asked to talk about their experiences of PSH. If this occurs, the qualitative researcher will follow the distress protocol (Appendix IV). If considered necessary, an outpatient appointment or telephone call will be arranged by the clinical team. However, this is extremely unlikely, as we do not propose to ask sensitive or difficult questions above what would routinely be asked by a stoma nurse.

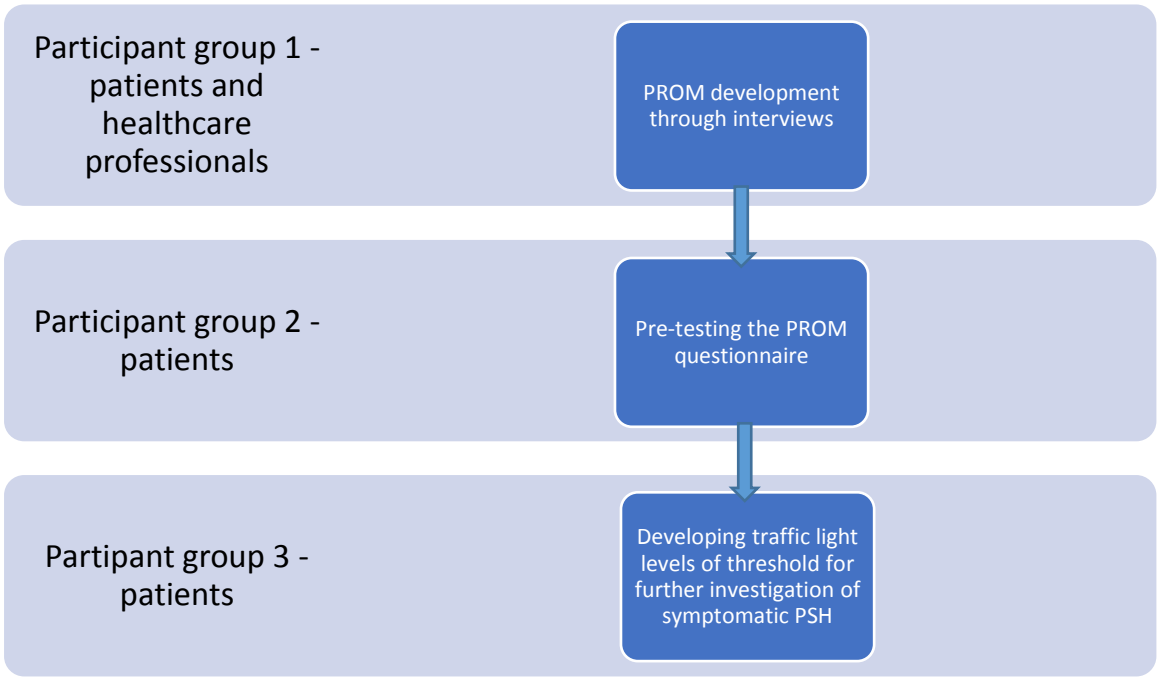
During the interviews if any PSHs or medical problems are detected that have not already undergone investigation the patient will be offered a clinical appointment with their normal team to investigate and discuss it further. Patients participating will have a letter (Letter 2: GP notification Interviews V1.0 19th April 2016) sent to their regular GP's to notify them of their study involvement should they be required to arrange further clinical follow-up and/or be required to make referrals (Appendix V).

The University of Bristol has 'Community based research guidance' lone worker policy. Accessible at http://www.bristol.ac.uk/safety/guidance/. The research team will strictly adhere to this guidance.

5.7 Frequency and duration of follow up

There is no planned participant follow up for Part 2 of Phase A.

FIGURE 2: Part 2 participant pathway flow chart



6. Ethics

This study will gain ethical approval from NHS REC prior to commencing research.

6.1 Confidentiality

Data will be marked with a unique study ID, patient initial and date of birth only. All personal identifiers will be removed from files including audio recordings and hard copy interview transcripts. Recordings will be transcribed by a University of Bristol employee or University of Bristol approved contracted transcribing service. All qualitative data will be

accessed only by members of the research team. No identifiable personal information will be included in any report that uses the data.

NHS research staff are required to follow the NHS code of confidentiality. All university research staff with access to personal data will hold an honorary NHS contract and be bound by the same rules of confidentiality as NHS staff.

6.2 Use of participant information

6.2.1 Use of personal contact details

These are required by the research team and research nurses to send initial invitation letters and PILs, and by qualitative researchers to arrange interviews. The research team will upload details of participants who have agreed to be contacted by the qualitative team on to a secure University of Bristol database. Qualitative researchers will be able to access this database so that they are able to make contact with potential participants and arrange a time to discuss the study in further detail. This database storing identifiable data will be a separate database from that containing interview recordings and transcripts. The database for the interview recordings and transcripts will be anonymised to include only study ID, DOB and initials.

6.2.2 Access to medical records by those outside of the direct healthcare team

In some cases members of the sponsor office at the University of Bristol staff (research staff) or the regulatory authorities may require access to the medical records of, or data collected about, patients entered into the study. The purpose of this access will be for auditing and monitoring research procedures in accordance with research governance procedures. Participants will be asked to consent to NHS, University and regulatory staff having access to their medical records for the purposes of the research study.

6.2.3 Use of digital devices/electronic transfer by computer network/storage on University computers

The interview conversations and case studies will be recorded so that the researchers can listen/watch to them again and make a written record (transcript) of discussions. Names will not be used and we will remove information that we think might mean that other people can recognise participants. Only the research team members will have access to the written accounts of the recordings. Digital recordings will be uploaded on to a password protected database stored on the secure computer server at the University of Bristol.

6.2.4 Use or publication of direct quotations from respondents

Any quotations from participants will be anonymised prior to publication.

6.2.5 Storage of personal details in manual files

Personal details will be recorded on the study paper eligibility forms. To minimise the risk of the incorrect form being completed for a study participant, they will be identified by the unique study ID and the participant's name. The forms of an individual participant will be held in folder which secures the participant's details from view and the individual patient folders will be stored in a secure location at each participating site (locked cabinet).

6.3 Loss of capacity

If a participant were to lose capacity during Phase A, the participant would be withdrawn from the study. Identifiable data already collected with consent would be retained and used in the Phase A. No further data would be collected or any other research procedures carried out on or in relation to the participant.

We have not specifically raised the issue of a loss of capacity in the PILs as we believe that it could be unnecessarily distressing to participants. However as specified above, participants who lose capacity during the study will be withdrawn from the study and the information leaflets (PIL 1 – 6) make it clear that if a participant withdraws, any information already collected about them will be used.

7. Study management

7.1 Planned study dates

Phase A will start April 4th 2016 and end April 3rd 2018

7.2 Sponsor

Phase A will be sponsored by the University of Bristol.

7.3 Day-to-day management

The study will be monitored and audited in accordance with the sponsor's policy. Further support will be provided by members of the MRC ConDuCT-II Hub for trials methodology research. The day-to-day running of the study will be managed by the research team at the University of Bristol. Specific training for staff in recruitment, consent and data collection will be provided by members of the research team at the School of Social and Community Medicine, University of Bristol.

7.4 Research governance

Phase A of the CIPHER study will be conducted in accordance with the Research Governance Framework for Health and Social Care and Good Clinical Practice. Phase A will be performed subject to NHS Research Ethics Committee (REC), Health Research Authority (HRA) and local NHS Trusts approval. Any amendments to the study documents will be approved by the sponsor prior to submission to the NHS REC and the NHS Trusts.

7.5 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been agreed to by all parties. Investigators are responsible for compliance to the protocol and the completion of data collection forms. Investigators will be required to read, acknowledge and inform the study team of any amendments to the study documents and ensure that the changes are complied with.

7.6 Indemnity

For NHS research HSG(96)48 reference no. 2 refers. If there is negligent harm during the study, then 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.

8. Data protection and participant confidentiality

8.1 Data handling, sharing and protection

Members of the research team, and representatives of the sponsor's office at the Trust, will have access to patient's medical records and personal information for the purposes of the Phase A. All such individuals will either be employees of participating trusts or University of Bristol employees who hold an honorary contract with these Trusts. Participants will be informed of this in the patient information sheet and asked to consent to this by signing the consent form.

Data will be collected and retained in accordance with the current data legislation. Audio interview recordings and digital video data capture will be uploaded within the hospital to a secure CTEU database and transferred securely to the SSCM, using a secure file transfer software package (e.g. nhs.net or Filezilla). Following upload and transfer, the data will be removed from the memory card/device immediately.

Interview recordings and digital video data capture will be held securely on password protected computers and networks at the SSCM. Both will be transcribed by a University of Bristol employee or University of Bristol approved contracted transcribing service. Data will be marked with a unique study ID, patient initial and date of birth only. All personal identifiers will be removed from all files including hard copy interview transcripts. All qualitative data will only be accessed by the members of the research team. No identifiable personal information will be included in any report that uses the data.

Field notes, unidentifiable baseline data and consent forms will be collected on study specific paper Case Report Forms (CRFs) by members of the study team. These completed CRFs will be taken to the SSCM along with the signed consent forms in envelopes clearly

marked as 'private & confidential'. Only data necessary to the purpose of the research will be obtained and stored.

8.2 Data storage

Interview recordings and video data capture will be held securely on password-protected secure databases within password-protected computers and networks at the SSCM. Appropriate access controls are in place such that only certain members of the research team can access the data. Study documents (paper and electronic) will be retained in secure locations at SSCM during and after the study has finished.

All hard copy study documentation will be retained in a secure location (e.g. locked filing cabinets) during the study and for 5 years after the end of the study. After this time, all patient identifiable paper records will be destroyed by confidential means. In compliance with the MRC Policy on Data Preservation, relevant 'meta'-data about the trial and the full dataset, without any participant identifiers other than the unique participant identifier, will be held indefinitely on the University of Bristol 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 (e.g. secure NHS hospital server).

Documents to interpret codes and personal data will be stored in separate encrypted files, in separate locations on the University of Bristol server. All hard copy study documents will be stored in locked filing cabinets and will not be removed from the University of Bristol or made available in any form to those outside the study. Identifiers will be separated at point of data entry at the SSCM.

9. Dissemination of findings

Phase A will be registered on a public database and a full report will be written for the NIHR on completion. Further dissemination of results will occur through publication in peer reviewed scientific journals, internal report, conference presentation, publication on websites and submission to regulatory authorities. Patient dissemination of results will be via the publications of the stoma associations and charities, e.g. Tidings Magazine and Ia News.

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Appendix I

PART 1: PROVISIONAL INTERVIEW TOPIC GUIDE - Healthcare professional's perspective on the surgeon's technique of stoma formation and on surgical risk factors for parastomal hernia (PSH) development

Opening

Interviewer will re-iterate study information, answer any questions, and take written consent.

(Check consent signed, recorder ON)

Background, interviewee details and ice-breaker

- Details of interviewee's current position and role, working history in clinical role, experience etc.
    - Define specialty experience i.e. specialist colo-rectal surgeon, general surgeon and grade of surgical experience, how often they perform stoma formations.

Stoma formation

- Could you describe - from start to finish - the stoma formation you performed*? (Prompt: Size, shape and location of incision, use of prophylactic mesh etc.)*
- Are there any factors that affected your choice of surgical technique *(Prompt: indication of surgery, previous scars etc)*
- In your opinion, which are the surgical techniques that are associated PSH formation *(Prompt: Why is that?)*
- In your opinion, which are the most important steps of in preventing PSH formation *(Prompt: Why do you think these steps are important)*
- When you review a new stoma, what would make you think it was done well?
- Do you think whether the procedure was performed as an emergency makes a difference to the risk of PSH formation
- Do you think whether the procedure was performed by a specialist or general surgeon makes a difference?
- Do you think whether the procedure was performed by a senior or junior surgeon makes a difference?
- Is there anything else you think that's important in preventing PSH that we haven't discussed?

Questions derived from non-participant observation

- "I noticed you did [observation]. Was there a reason for that?"
- "What do you think the result of [observation] will be?"

Closing

Interviewer checks consent taken, checks understanding of any outstanding points, answers further questions, and checks to see if interviewee would like to receive a summary of findings.

(Thank you, Recorder **OFF)**

Comments:

Appendix II
Part 2: PROVISIONAL INTERVIEW TOPIC GUIDE HEALTHCARE PROFESSIONALS - Perspectives on symptoms and problems associated with parastomal hernias (PSH).

Opening
Interviewer will re-iterate study information, answer any questions, and take written consent.
(Check consent signed, recorder ON)

Background, interviewee details and ice breaker

- Details of interviewee's current position and role, working history in clinical role, experience etc.
    - For surgeons: Define specialty experience i.e. specialist colo-rectal surgeon, general surgeon and grade of surgical experience, how often they perform stoma formations.
    - For stoma nurses: Explore the history of clinical experience and range of patients cared for.

Explore the healthcare professional's experiences of Parastomal hernias
Begin with open questions *(e.g. What do you consider to be the problems of living with a PSH? What do you think patients consider to be the problems of living with a PSH?)*

Further probing to explore the healthcare professional's experiences of Parastomal hernias:

- Day-to-day symptoms of living with a PSH? *(Prompt: What are the day-day problems of living with a PSH? E.g. Pain and skin problems)*
- Day-to-day signs of living with a PSH *(Prompt: What are the physical signs might you see if a patient has problems with a PSH? E.g. Swelling, redness, empty bag)*
- Life-threatening problems/problems warranting emergency admission *(Prompt: What are the symptoms/signs of the life threatening problems of a PSH? When would you consider emergency admission? E.g. Symptoms/signs of strangulation, perforation, obstruction)*
- Symptoms/signs/problems that would warrant referral for an outpatient clinic *(Prompt: What are the symptoms/signs of problems that you would consider to be an indication for an outpatient clinic/repair of the PSH?)*
- Quality of life issues of with living with a PSH *(Prompt: In what way can having a PSH affect the patients' quality of life? E.g. Smell, leakage fears, time costs)*
- Social problems of living with a PSH? *(Prompt: In what way can a PSH affect the patient's social life? E.g. Limitations to work, time costs, financial issues, sexual issues, social issues)*
- Additional support needs *(Prompt: e.g. Are there any additional support needs for those living with a PSH? E.g. Carers, family/friend support, GP appointments, referrals to clinic, referrals to A&E, stoma nurse follow-ups, district nurse follow-ups, social work, emotional support, psychological support)*
- Financial issues to living with a PSH? *(Prompt: Are there any additional financial issues for those living with a PSH? E.g. Cost of bags, cleaning, laundry)*
- Emotional issues to living with a PSH? *(Prompt: Are there any emotional issues for those living with a PSH? E.g. Depression, relationship problems, social anxiety)*

- Work related issues to living with a PSH? *(Prompt: Are there any work related issues for those living with a PSH? E.g. Disability days, change in responsibilities, confidence in the work place)*
- Ability to participate in normal activities? *(Prompt: Can having a PSH affect the patient's ability to participate in normal activities? E.g. Shopping, exercising, socialising, enjoying family time, maintaining relationships)*

Explore the professional's experiences of PSH

- Degree of variation in PSH presentation *(Prompt: What do PSH's look like? How often are they symptomatic or asymptomatic?)*
- Level of experience with parastomal hernias *(Prompt: How often do you look after patients with a PSH? E.g. Weekly contact, monthly contact, rare contact, no contact)*
- The professional's initial assessment *(Prompt: When you see a patient who you suspect may have a PSH, what questions do you ask?)*
- Severity assessment *(Prompt: How would you assess the severity of the PSH e.g. using Scaling items such a pain scale)*

Symptoms of stomas separate to those of living with a PSH

- Explore the symptoms separate to stomas that patients living with or without a PSH may experience (Probe: Are there any symptoms specific to stomas that the patient would experience that aren't caused by the PSH? E.g. Loose stools, dehydration)

Closing

Interviewer checks understanding of any outstanding points, answers further questions, and checks to see if interviewee would like to receive a summary of findings.

(Thank you, Recorder **OFF)**

Comments:

Appendix III

Part 2: PROVISIONAL PATIENT INTERVIEW TOPIC GUIDE - Perspectives on symptoms and problems associated with parastomal hernias (PSH).

Opening

Interviewer will re-iterate study information, answer any questions, and take written consent.

- Interviewer self introduction
- CIPHER Phase A Part 2 aims to:
    - Understanding your experience of living with a stoma with or without a PSH
    - To explore what's important to you, in regards to you symptoms/problems of living with a stoma with or without a PSH
- Any questions?
- Okay to record? Take written consent

(Check consent signed, recorder ON)

Background, interviewee details and ice breaker

- Interviewee background
    - Just to give me some background, can you just tell me a little bit about what type of stoma you have? *(Procedure: When? Where? Why? Elective/emergency?)*
    - Can you tell me about your stoma, have you had any problems with your stoma or the area around your stoma? *(Prompt: Any problems, have you needed to seek professional help?)*

Experiences of living with a stoma

- In terms of stoma symptoms or problems did you have any expectations before your surgery? *(Prompt: Where did these come from?)*
- How has stoma/area around the stoma been? *(Prompt:* Any issues/complications?*)*
- How have you found managing your stoma and the area around your stoma? *(Prompt: What liked?)*
- Have you had to go back to hospital because of any problems with the stoma or area surrounding the stoma? (*Prompt: Have you needed to go back to theatre or see your surgeon or stoma nurse for any problems?)*
- Do issues relating to your stoma, or area around your stoma, bother or worry you on a day-day basis? (*Prompt: Commonly experienced problems such as pain, redness or skin problems)*
- Are there any quality of life issues related to the stoma, or area around your stoma? *(Prompt: In what way can having a stoma affect your quality of life e.g. smell, leakage fears, time costs)*
- Do issues relating to your stoma, or area around your stoma, affect your social life*? (Prompt: Limitations to work, time costs, financial issues, sexual issues, social issues)*
- Do you have any additional support needs because of issues relating to you your stoma, or area around your stoma? *(Prompt: e.g. Carers, family/friend support, GP appointments, referrals to clinic, referrals to A&E, stoma nurse follow-ups, district nurse follow-ups, social work, emotional support, psychological support)*

- Are there any financial issues related to your stoma, or area around your stoma? *(Prompt: Cost of bags, cleaning, laundry)*
- Do you find that issues with your stoma, or area around your stoma, affects you emotionally? *(Prompt: Such as depression, relationship problems, social anxiety)*
- Are there any work related issues with your stoma, or area around your stoma? *(Prompt: Disability days, change in responsibilities, confidence in the work place)*
- Does your stoma, or area around your stoma, affect your ability to participate in normal activities? *(E.g. Shopping, exercising, socialising, enjoying family time, maintaining relationships)*
- Are you known to have a PSH?

Persepectives of questionnaire

We are developing a questionnaire that aims to understand patients' of living with a stoma that may or may not be complicated by the presence of a parastomal hernia.

- Would you kindly complete this questionnaire and comment on how understandable the questions are and whether you think the questions cover all symtpms and problems of having a stoma/PSH.
- Can you add anything?

Closing

- Summarise key points
- Any further questions?

(Thank you, Recorder **OFF)**

Comments:

Appendix IV: Distress protocol: Interviews

All interviews will be prefaced with a statement about confidentiality and the duty of care. Participants will be told that the interview is strictly confidential but should they disclose information to suggest that they are at significant risk of harm the researcher may have to discuss this with a clinical advisor.

In the event that a participant appears to be distressed during the interview (for example, becomes silent or begins to cry) or discloses information to provoke concern about suicide risk, the following procedures will be followed:

1. Participants will be offered the opportunity to pause for a break from the interview and will be asked if they would like to resume the interview
2. If necessary, the interview will be terminated and recording equipment will be stopped
3. At first, the interviewer will listen to the interviewee and offer support in situ. This will allow the researcher to assess whether further action is required
4. Should the interviewer remain concerned, they will reflect this to the interviewee and, depending on the nature of the situation:
    a. Offer information about local sources of help
    b. Ask the interviewee if there is anyone they should contact, and if so attempt to make contact
    c. Offer to make initial contact with clinical services (primary or secondary care) on behalf of the individual and with their consent
5. In cases of particular concern, the interviewer will
    a. If necessary, remain with the person until their distress has subsided or someone else is present
    b. Contact a local study clinician for advice or assistance
    c. Provide a written report of the incident to the principal investigator including information about the nature of the distress and the actions taken

Interviewees will be advised to contact their GP should they subsequently find that the interview provokes issues that they need to discuss.

Appendix V: Letter 2: GP notification Interviews

The CIPHER Study
University of Bristol
School of Social & Community Medicine,
Canynge Hall
39 Whatley Road
Clifton, Bristol
BS8 2PS

Private and confidential

Dear General Practitioner,

Re: <insert patient name, date of birth & address>
We would like to inform you of the above patient's involvement in the UK Cohort study to Investigate the prevention of Parastomal HERnia (CIPHER) Phase A. We will be interviewing the above patient about living with a stoma. During the interviews if any parastomal hernias or medical problems are detected, that have not already undergone investigation we may write to you to request that a clinical appointment with yourself or their normal team be made to investigate and discuss it further.
This study is being run by the University of Bristol in conjunction with the Royal Devon and Exeter & University Hospitals Bristol NHS Foundation Trusts.
Please contact us with any concerns,

Yours faithfully,

Professor J Blazeby BSc, MB ChB, MD
Chief investigator of the CIPHER study Phase A,
Professor of Surgery at the University of Bristol
Consultant Upper GI Surgeon at the Bristol Royal Infirmary

Appendix VI: Letter 3: GP notification case studies

The CIPHER Study
University of Bristol
School of Social & Community Medicine,
Canynge Hall
39 Whatley Road
Clifton, Bristol
BS8 2PS

Private and confidential

Dear <insert GP name>

Re: <insert patient name, date of birth & address>
We would like to inform you of the above patient's involvement in the UK Cohort study to Investigate the prevention of Parastomal HERnia (CIPHER) Phase A. We will be observing and digitally recording the above patient's stoma formation in theatre.
This study is being run by the University of Bristol in conjunction with the Royal Devon and Exeter NHS Foundation Trust, University Hospitals Bristol NHS Foundation Trust and University Hospital Birmingham NHS Foundation Trust.
Please contact us with any concerns,

Yours faithfully,

Professor J Blazeby BSc, MB ChB, MD
Chief investigator of the CIPHER study Phase A,
Professor of Surgery at the University of Bristol
Consultant Upper GI Surgeon at the Bristol Royal Infirmary

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

IRAS No: 210716
REC No: 17/WM/0401
ISRCTN No: ISRCTN17573805
NIHR Project No: 14/166/01

Details of Sponsor

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Table of contents

This study is funded by the NIHR Health Technology Assessment Programme (Ref 14/166/01). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Glossary / abbreviations

ACPGBI	The Association of Coloproctology of Great Britain and Ireland
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computerised Tomography
CTEU	Clinical Trials and Evaluation Unit
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
SEG	Study Executive 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

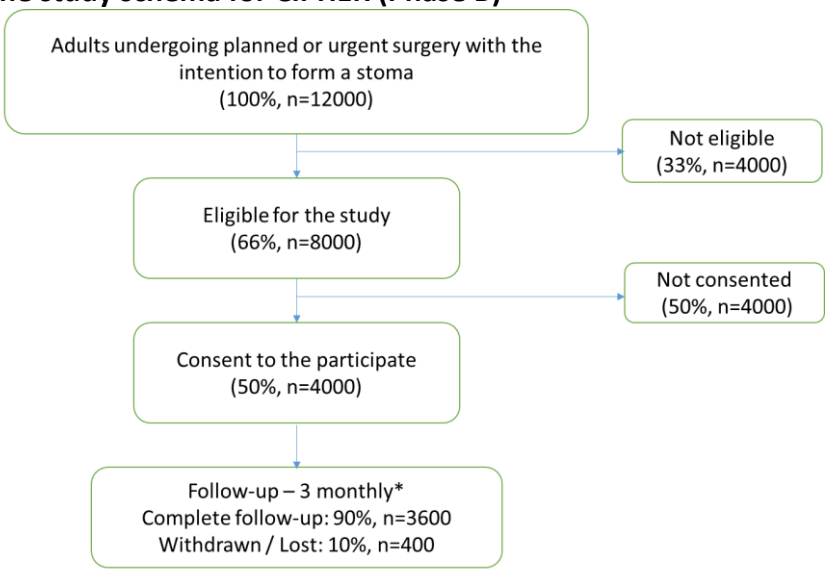
The CIPHER study (Phase B; CIPHER-B) aims to establish the incidence of symptomatic and radiologically confirmed PSH during a minimum of 2 years follow up. Additionally, CIPHER aims to evaluate the effects of key technical surgical steps during index stoma formation on the risk of subsequent PSH formation.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

1. To describe the incidence of PSH formation within 2 years of formation of all types of stomata other than loop ileostomies;
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)



*The duration of follow-up is for a minimum of 2 and maximum of 4 years

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*
- Anatomical PSH, ascertained by independent reading of a CT scan (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.

CT scans carried out in the course of a patient's usual NHS care will be assessed for all participants, with anatomical PSH being graded using the EHS classification (EHS class I, II, III or IV [24]). CT scans taken up to 6 months before or 3 months after the stoma questionnaire is completed will be valid for assessing anatomical PSH. The combination of symptomatic PSH and anatomical PSH confirmed by CT imaging will be our primary outcome. CT assessors will collect additional details from CTs (e.g. linear measurement of the PSH defect rather than just defect size >5cm vs ≤5cm), including a measure of the size of the PSH. The ESH criteria for classifying PSH as small or large will be reviewed on the basis of these additional data as the study progresses.

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. Generic health status (EQ-5D-5L, SF12 [38, 39]), which will be combined with survival to estimate QALYs
7. Appointments with SCNs, stoma care products used and associated costs
8. PSH repair (procedure codes for stoma formation in HES, information from SCNs) and associated hospital costs
9. 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. In practice, 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 planned closures of loop ileostomies). These factors will be monitored as data accrues for the study, 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%).

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*Error! Reference source not found.). 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**.

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.

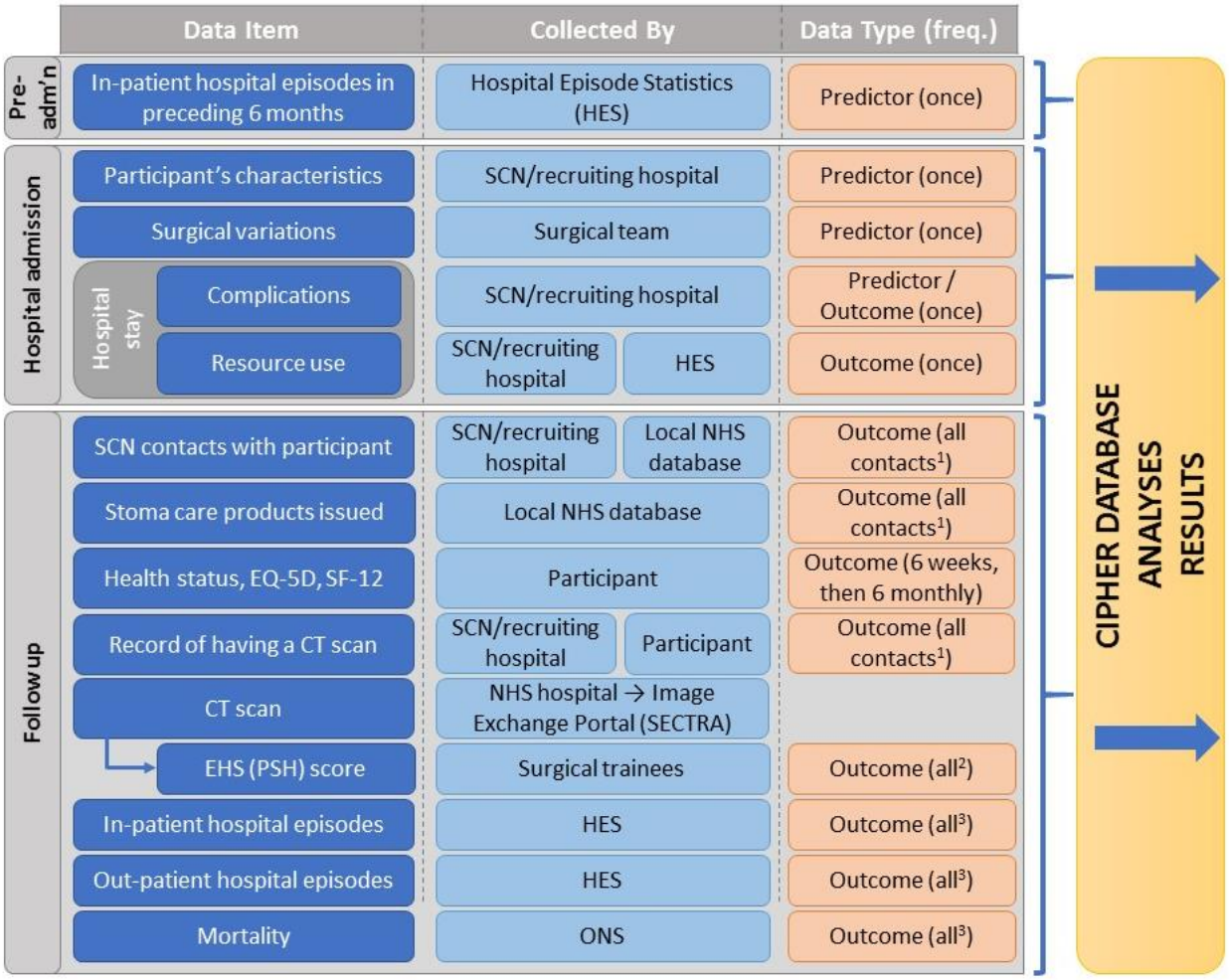
5.3 Definition of end of study

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 periodically.

Table 4: Timing and frequency of collection of data items

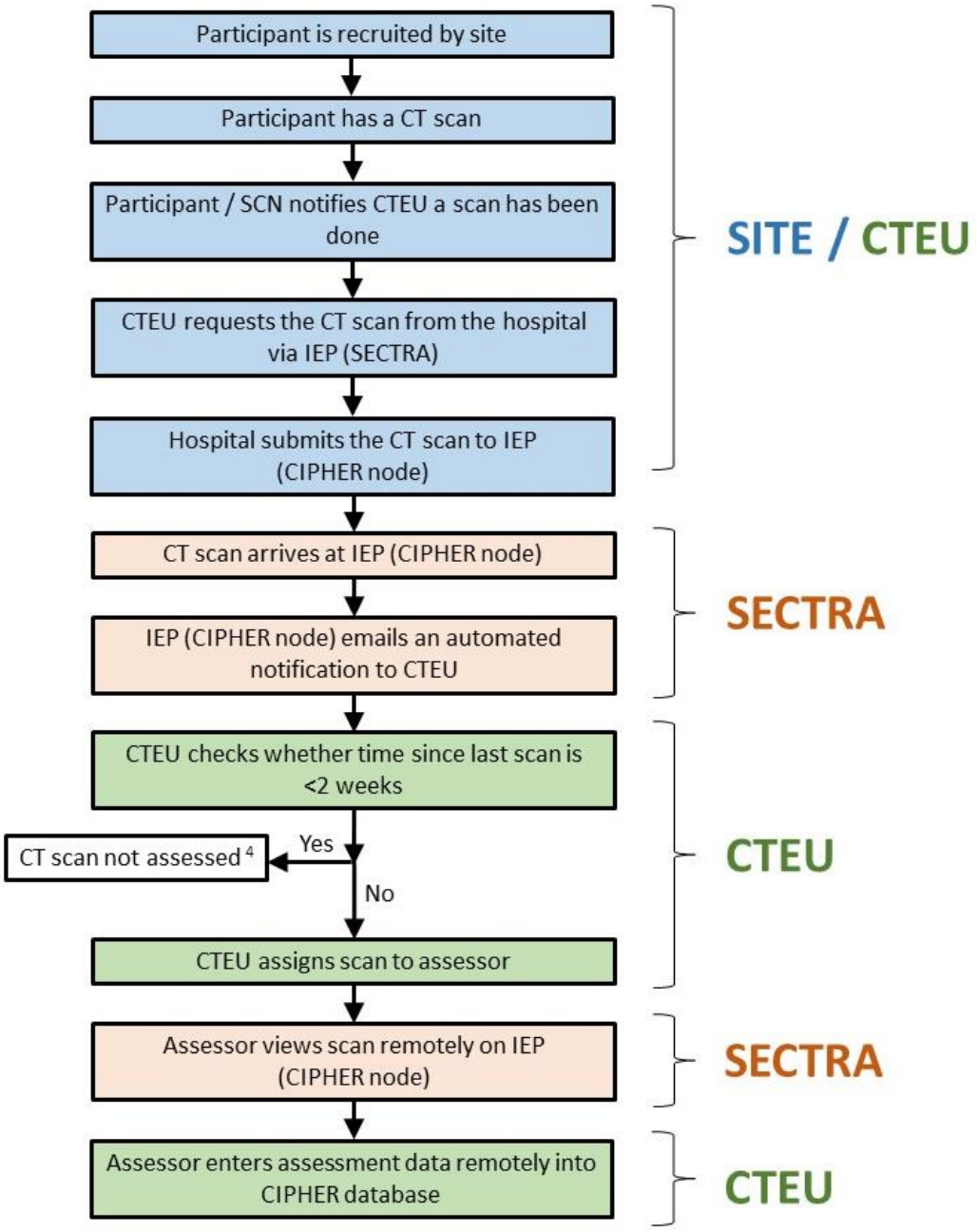
	Time / frequency of data collection with respect to date of index surgery						
	Before	**During**	**Up to discharge**	**6-weeks after**	**6-month after**	**12-month after**	**6-monthly to study end**
Screening log	✓						
Consent form	✓						
Participant baseline details	✓						
Surgical details		✓					
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 periodically throughout 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. 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 from periodic linked extracts of Hospital Episode Statistics (HES) data, from NHS Digital.
(j) Information about participants who die during the study will be obtained from the periodic 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 / image exchange portal



5.5 Assessment of CT scans

Volunteer surgical trainees (members of Surgical Trainee Collaboratives, STCs) will be recruited to assess CT scans (see 6). They will be trained (see 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 viewed through the IEP (CIPHER 'node' hosted by Sectra Ltd, provider of the IEP to the NHS in the UK). EHS classifications that differ by ≥2 EHS grades will be adjudicated by an expert adjudicator. 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 0). 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 (CTEU Bristol).

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 submitted to the CIPHER 'node' hosted by Sectra 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 IEP, 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 CTEU 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.

Exploratory analyses will be used to inform the choice of survival distribution (e.g. Weibull). The factors included in the model, the modelling strategy and the approach to handling correlated covariates will be documented in the statistical analysis plan. 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 a redo stoma 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 models, 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.

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 (e.g. biologic, synthetic) versus no prophylactic mesh in preventing PSH and improving health related quality of life. The intervention groups to be compared will be finalised after recruitment so that they consist of clinically and economically similar interventions in common clinical use. A detailed health economics analysis plan will be prepared prior to locking the database [44].

The primary economic evaluation will be a cost-utility analysis from the NHS perspectives. A secondary analysis will be from a broader perspective (social care, personal costs). We will conduct the primary evaluation at 2 years after index surgery. We estimate that 30% to 40% of participants will have developed a PSH, allowing major differences in the post-surgical cost between the options for different types of mesh to be detected. If differences in the incidence of PSH, quality of life or stoma care costs over 2-years indicate that interpretations of cost-effectiveness might be sensitive to the duration of follow up (e.g. expensive interventions might become cost-effective in the longer term) we will also carry out an evaluation over a lifetime horizon making assumptions about the trajectory of PSH incidence, PSH repair, on-going stoma care costs, QALYs and survival.

NHS costs include those associated with (i) the operation (ii) the post-operative in-patient stay and (iii) stoma care and PSH repair during follow-up. As the insertion of mesh accounts for only a small fraction (5-10 minutes) of the whole procedure, the predominant differential cost of using mesh during the index procedure is the cost of the implant itself. We will estimate the unit cost of mesh based on the purchase price at a range of hospitals participating in the study. We will use NHS reference costs (including excess bed day costs) to estimate the cost of the index hospitalisation, based on length of stay. Subsequent stoma care contacts and products, and stoma-related primary and social care use will be costed using nationally published sources. Information on subsequent in-patient (e.g. PSH repair) and out-patient hospital care from HES will costed using NHS reference costs [45-47].

The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs) estimated using the EuroQol EQ-5D 5L [38] which will be administered at baseline, 6 weeks post-surgery and subsequently at 6 monthly intervals by post or online. We will

estimate the cumulative cost, QALY and net monetary benefit for each patient. Net monetary benefit regression will estimate the association between cost-effectiveness and mesh type, adjusting for a range of potential confounders (i.e. patient characteristics, open/laparoscopic surgery). Uncertainty will be addressed in sensitivity analyses and by using bootstrapping to estimate a cost-effectiveness acceptability curve. Costs and benefits beyond the first 12 months will be discounted in line with recommendations [48].

9. Study management

The study will be managed by the Bristol Clinical Trials and Evaluation Unit (CTEU) of the University of Bristol. The CTEU Bristol is a UK Clinical Research Collaboration registered Clinical Trials Unit. The CTEU Bristol 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 Executive Group (SEG), 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 CTEU Bristol. 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 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
- Michael Seres, 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 [49].

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 CTEU Bristol 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 1998.

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 CTEU Bristol 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.

Other than the data sharing specified above, no study data will be made available for sharing until after publication of the main results. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary 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 secondary research, e.g. 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