



The PITSTOP Study: Pilonidal sinus Treatment: STudying the OPTions

An observational cohort with nested mixed methods and qualitative design to investigate surgical options for the treatment of pilonidal sinus disease.

Version 1.1; 12th November 2018



Chief Investigator: Steven Brown, Sheffield Teaching Hospitals NHS Foundation Trust

Sponsor reference: STH20008

HTA reference: 17/17/02

University of Sheffield reference:

REC reference: TBC

NRES:

ISRCTN:

Authorised by:



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Abbreviations

ACPGBI	Association of Coloproctology of Great Britain and Ireland
AE	Adverse event
ATET	Average treatment effect among the treated
CI	Chief Investigator
CRF	Case report form
CTRU	Clinical trials research unit
DCE	Discrete Choice Experiment
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
PD	Pilonidal disease
PI	Principal Investigator
PPI	Patients and public involvement
PSC	ProjectSteering Committee
R&D	Research and Development
RCT	Randomised control trial
REC	Research ethics committee
SAE	Serious adverse event
ScHARR	School of health and related research
SOP	Standard operating procedure
STH	Sheffield Teaching Hospitals
TMG	Trial management Group

1. Project Details

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1.3 Title of project

An observational cohort with nested mixed methods and qualitative design to investigate surgical options for the treatment of pilonidal sinus disease.

Short title:

The PITSTOP Study: Pilonidal sinus Treatment: STudying the OPTions

1.4 Sheffield Teaching Hospitals project reference number

STH 20008

1.5 Protocol version number and date

Version 1.1, 12th of November 2018

1.6 Sheffield Teaching Hospitals Directorate affiliation

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2. Research Questions

1. What are the different subtypes of pilonidal disease for which the various treatment options are indicated?
2. What combinations of excision and closure techniques are used?
3. Which outcomes do patients value and which interventions do they prefer?
4. What further research is needed?

3. Abstract

A pilonidal sinus is an infected tract under the skin between the buttocks. Despite being a common condition there is no consensus as to how to manage pilonidal disease. Available data indicates hugely varied practice throughout the UK. The literature for guiding optimal management is hampered by the lack of a universally accepted classification of disease, multiple potential interventions with no indication of clinical equipoise for these interventions or whether comparative studies are feasible. In addition, it is unclear what outcome measures are relevant to patients, which can be easily and reliably measured and are sufficiently sensitive to change. We propose a prospective cohort study to determine the subtypes of pilonidal disease for which the various treatment options are indicated, to describe the various interventions, to engage with patients and determine which outcomes they value and which interventions they prefer/do not prefer and to provide recommendations for further research.

To identify healing rates, recurrence and re-intervention, we will recruit consecutive, consenting adults with pilonidal sinus, considered suitable for surgery in 15 NHS trusts with large pilonidal practices. Classification will be by anatomy/pathology of pit and tracks. We will record method of excision (minimal, major, curettage) and closure (none, midline, lateral, flap, glue, phenol injection). Although 18 combinations of intervention are theoretically possible, not all are commonly used. We will record the following outcomes: wound healing (complete closure of the skin with no residual drainage or symptoms); infection; recurrence; post-operative pain rating; EQ-5D-5L; return to normal activities; interactions with primary care. Risk models that predict healing and recurrence will be built for each treatment pathway. We will stratify outcomes by severity of disease: propensity score matching of patients (based on patient characteristics and pit anatomy/pathology at screening) will be used to estimate risk-adjusted outcomes for each treatment pathway. The study aims to consent n=800 over 15 months. We anticipate this will result in approximately 100 participants per front running

strategy which will enable us to estimate proportions to a standard error of $\leq 5\%$, and pain to within a standard error of 0.2 points of a 10-point scale. A pilot phase with a formal stop/go recruitment target will ensure that sufficient numbers will be recruited in order to ensure at least 100 in the front running treatment strategies. All treatment groups will continue to be included after the pilot phase in order to describe what combinations of excision and closure techniques are used. Treatment strategies with low numbers will be excluded from the comparative analysis but will be reported descriptively

To get an overview of patient views and experiences as well as assess which interventions patients would rather avoid and which outcomes are they most value, we will conduct brief semi-structured interviews (n=20) as close as possible to the procedure (preferably prior) and six months after the procedure. Patients will be sampled for maximum variation based on pit/track anatomy and excision / closure methods. Interviews and Framework analysis based on relevant sections of published decision-making and acceptability frameworks. Analytic strategies (triangulation etc.) will be used to integrate qualitative and quantitative data.

To assess which interventions patients would rather avoid and which outcomes they most value. Semi-structured interviews will be used to identify key attributes (e.g., wound infection) and levels (e.g., no infection, needing antibiotics, and needing operation) important to patients. The Discrete choice experiment will be administered to n=300 cohort participants. Quantitative analysis will reveal how much patients value different outcomes, and estimate patients' relative utility and willingness to trade between outcomes.

A consensus regarding the sub-groups of patients for whom the various interventions may be suited will be generated, along with a consensus working with clinicians and patients, together with a consensus meeting defining appropriate comparators and valued outcomes for any future randomised controlled trial. To do this, a modified nominal group technique consensus exercise will be undertaken. This will take place over half a day, adjacent to the annual Association of Coloproctology of Great Britain and Ireland (ACPGBI). It will be opened to around 40 colorectal surgeons and around 15 patients from across the UK.

4. Objectives of the Study

In order to answer the research questions posed above we will:

1. Follow patients with symptomatic pilonidal sinus referred to each collaborating site, prospectively recording details of their pit / track anatomy, surgical management, medical events, health-related quality of life until six months after their operation.
2. Describe the combination of interventions currently in use and quantify clinical and patient-reported outcomes associated with each.
3. Identify patient-specific disease features that might predict poor outcome in each treatment group by risk-modelling methods.
4. Derive a case-mix adjusted estimate of the risks associated with common treatment options, using causal inference methods to provisionally rank the optimal management strategies among patients for whom more than one treatment is considered appropriate.
5. Provide an overview of patient views and experiences.
6. Collect the views of patients on which interventions they would rather avoid and which outcomes they most value.
7. Reach a surgeon-based consensus on which subtypes of pilonidal disease may benefit from which treatment options
8. Reach a surgeon and patient-based consensus on research priorities.

5. Background

Pilonidal disease (PD) is a common condition that affects about 26/100,000 of the population, predominantly young, working people(1). The term pilonidal derives from the Latin words for hair (pilus) and nest (nidus). It is an acquired disease resulting in obstruction of hair follicles in the natal cleft (the anatomical groove between the buttocks). Subsequent rupture of the follicles leads to abscess and sinus formation. Risk factors for development of the condition include male gender, extensive body hair in some patients, young adulthood, family history, local trauma, sedentary lifestyle, poor hygiene, an anatomically deep natal cleft and obesity(1)(2)(3). Once established the condition persists and progresses through insertion of ingrown or loose hairs into the sinuses (2)(3). The term PD encapsulates a wide spectrum of abnormalities ranging from relatively asymptomatic simple sinuses to complex abscess cavities with multiple sinus tracks that persist despite repeated surgical intervention. Individuals present either as an emergency with a painful abscess between the buttocks or electively with a chronic cycle of pain and discharge from the sinuses, causing disruption to work, relationships and quality of life(4)

The ideal management of PD should be simple, safe, cost effective, easy to perform and lead to a rapid return to normal activities, with low rates of acute wound complications (including infection, seroma, haematoma), recurrence, and rapid wound healing. These aims are not reliably delivered by current surgical practice and there is no consensus on how to manage based on disease characteristics.

There is currently no effective treatment for early, asymptomatic PD. Individuals with simple sinuses have little option but to wait for deterioration in their clinical condition before surgical intervention is considered appropriate. This clinical algorithm likely reflects the perceived ineffectiveness of existing surgical treatments combined with the substantial morbidity associated with their failure.

Emergency presentation of pilonidal abscess requires hospitalisation with incision and drainage of the abscess cavity. One in five patients present with recurrent symptoms following emergency surgery(5). This picture of relapsing and remitting infections is typical of chronic PD.

Treatment of chronic PD is surgical using usually two essential components (the exception being phenol injection and fistuloscope/diathermy-which aim to induce fibrosis and obliterate the tracks), with again no clear consensus as to which approach for each component is best. These components include excision of affected skin and fat (the amount of which varies among patients and surgeons) and differ in respect to how the resultant wound is managed. Either the wound is left open and heals slowly by secondary intention or the skin is closed using sutures, also known as primary wound closure.

The skin closure technique may be midline or off-midline. In the off midline technique, the wound is positioned adjacent to the natal cleft, rather than in the natal cleft itself in order to theoretically aid healing(6). Examples include the Karydakis flap, Bascom II technique, Rhombic and Limberg flaps. While selected single centre cohort studies for all these techniques have reported very low recurrence and infection rates it has proven difficult to replicate these results across health services. Wound breakdown/ dehiscence is a particularly problematic complication following this type of operation as patients may not be capable of returning to work for several months(7).

Fibrin glue is an alternative method of closure and is certainly less invasive than the excision techniques. Treatment involves curettage of sinus tracts to remove debris before they are sealed by injection of fibrin glue. This biological scaffolding fills the sinus and over time is gradually

replaced by the patient's own tissues. The avoidance of large painful wounds and the need for dressings are an advantage over other techniques but quality data about recurrence is lacking(7)(8)(9).

5.1 Monetary and humanistic burden

The condition is relatively common and represents a significant burden to primary and secondary care in the NHS 2012 Hospital Episode Statistics (HES) data reported 13,239 hospital admissions for PD(10). At present, both emergency and the most common elective excisional surgical treatments leave large open wounds that take months to heal(6)(7). Patients consequently require prolonged wound care from their community services. As the disease tends to affect young otherwise healthy adults, this prolonged need for dressings and general wound care impacts on education, work, intimacy and social life, pain, recurrent infection and fear of wound deterioration all severely affecting quality of life(11)(12).

5.2 Knowledge gap

The optimum treatment that is both easy to perform and results in rapid healing and minimal complications is not clear. This is reflected in a perceived varied practice throughout the UK. Indeed, some procedures result in lengthy healing times and long periods of incapacity. The literature on PD is large but mainly consists of single-centre cohort studies looking at individually favoured techniques. Many of these series have reported very low recurrence and infection rates for almost all procedures. It has proven difficult to replicate these results in 'real life'.

Much data on PD consist of single cohort studies, which make no attempt to stratify patients, the extent of disease or the adjuvant management (antibiotics, anaesthetic, post-operative care). There have been some Randomised controlled trials (RCTs), which are summarised in 2 Cochrane reviews. The first showed that healing through secondary intention had lower overall recurrence rates compared to primary closure but at the expense of longer healing times(13). A previous systematic review reached the same conclusion but also compared two types of closure, suggesting off-midline to be preferable to midline (14). The authors also concluded outcome measures, such as time to healing, were poorly analysed, health economic data was lacking and that future trials should be adequately powered, multicentre and include valid methods of assessing surgical outcomes. A third systematic review of wound care after pilonidal excision found no best practice guidelines and only one clinical pathway(15).

The second Cochrane Review focused on fibrin glue in the treatment of PD (16). The authors concluded this was a promising and appealing option as monotherapy given the non-invasive nature and that it could be performed as a day-case procedure, under local anaesthesia. These conclusions echo the conclusions of a previous meta-analysis, both suggesting a need for further research(17). Nevertheless, the research to date has largely considered fibrin glue as an adjunct to surgery and although small, single centre observational studies(8)(9)(18)(19)(20)(21) have been published, there is no RCT of fibrin glue as monotherapy in treatment of PD.

In summary, there is a lack of evidence regarding classification of disease, what are the front running interventions, whether there is clinical equipoise for these interventions and whether comparative studies for these interventions are feasible in terms of recruitment and finally what outcome measures are relevant to patients, can be easily and reliably measured and are sufficiently sensitive to change.

6. Plan of Investigation

6.1 Methodology

The trial will be co-ordinated from the Clinical Trials Research Unit (CTRU) in Sheffield School of Health and Related Research (SchHARR). Delegated study staff located at individual centres will identify and consent potential participants.

Prior to the commencement of the cohort study there will be a survey circulated within the colorectal consultant surgeon network. The survey will be distributed via email throughout the trainee surgeon network and will be completed in paper and pencil format by consultant colorectal surgeons. This survey will seek to determine the methods of surgery currently employed in the field and the ways in which the surgeon learned this technique. The survey will also explore the factors affecting choice of treatment method in relation to disease presentation. Finally, it will seek to investigate the estimated mean recurrence rate for each surgeon. Currently, there is a lack of evidence outlining the general practice of treatment for pilonidal sinus in the UK. This survey will provide evidence on the techniques currently in use in the UK Health Care system.

For the cohort study, potential participants will be aged >16 years listed for elective surgical treatment of pilonidal disease. Patients considered suitable for surgery will be identified from GP or secondary care referral, sent a patient information sheet about the study, detailing the study and all treatment options, and diverted preferably to a specific recruiting clinic. At the clinic, a member of the research team will explain the study to the patient and give them the opportunity to ask any questions. The Principal Investigator or delegated research team member will confirm eligibility and ensure written informed consent is obtained before any patient data is collected. Participants will be advised that they are able to withdraw from the study at any point without any impact on their routine NHS care. As is standard practice, the surgeon will discuss the condition, possible interventions and their advantages and disadvantages. Each participant will be invited to answer a questionnaire on shared decision making (CollaboRATE)(22).

Potential participants will fall into the following groups:

1. Patients presenting to the surgical outpatient clinic with symptomatic pilonidal sinus that do not require further tests. This group will be identified by the clinical team from the GP referral letter and a patient information sheet sent to them prior to their clinic appointment. If they are willing to participate they will be consented when they attend the appointment.

2. Patients presenting to the surgical outpatient clinic with symptomatic pilonidal sinus that require further tests to exclude other diagnoses. This group will be identified by the clinician at the clinic appointment and given a patient information sheet. They will undergo the necessary outpatient tests and if negative and the symptoms are due to pilonidal sinus they will be contacted by the research nurse prior to attending their follow-up clinic appointment. They will then be randomised and consented when they re-attend the clinic.

Thus, in each group, there is opportunity to provide the patient information sheet prior to a clinic appointment; patients will have a minimum of 24 hours to decide whether they wish to take part. Patients with investigations excluding pathologies other than pilonidal sinus will be contacted by the research nurse before the planned follow up clinic to ascertain whether they meet entry criteria and are interested in entering the study. They will then be seen by the consultant and research nurse in clinic where recruitment and consenting will take place.

The operative intervention will be according to the surgeon's usual practice with details collected by the surgeon on a specifically designed case report form (CRF). The CTRU will co-ordinate follow-up and data collection in collaboration with the UK centres. Participant study data will be collected and recorded on relevant CRFs and patient questionnaires and then entered onto a remote web-based data capture system, transferring data to Sheffield CTRU for analysis.

For all of the cohort patients, data will be collected to establish which patients have further treatment for recurrent symptoms or complications following their initial procedure. This will be achieved at the six-week clinic visit following the intervention and by interrogating hospital records, asking the patients' consultants, writing to patients' GPs and questioning the patient via telephone interview at 6 months and at the end of the study. At this stage each participant will also be invited to complete a questionnaire on decision regret(23).

A proportion of patients (n=20) will be randomly selected and asked to take part in the nested mixed methods sub study. For the participants' comfort and convenience, we will collect data by telephone or Skype. Consent will be taken over the phone prior to the interview commencing. To assess which outcomes are most valued by patients, and whether there are particular interventions they would rather avoid, the baseline interview guide will adapt key questions from the CODE framework(24): At six months, the topic guide will ask further modified CODE questions. At each time point-probing questions will be used to ensure coverage of relevant generic dimensions of acceptability(10) and to identify important

attributes of interventions and levels of value they might place on those attributes, to inform the discrete choice experiment (Section 6.3.3). Interviews will last 30-40 minutes at baseline and 10 minutes at six months.

The data from these interviews will be used to construct a discrete choice experiment. All consented patients will be sent a link to their email addresses via Qualtrics, containing a participant information sheet and simple instructions on how to complete the choice questionnaire. The questionnaire will contain hypothetical choice scenarios (typically range from 8-12 choice sets to avoid cognitive burden) and will ask patients to make choices between two combinations of outcomes with varying levels. The questionnaire should take no more than 15 minutes to complete. Demographic data will be extracted from the cohort database, minimising participant burden.

At the end of the cohort study a consensus regarding the sub-groups of patients for whom the various interventions may be suited will be generated, along with a consensus working with clinicians and patients, together with a consensus meeting defining appropriate comparators and valued outcomes for any future randomised controlled trial. To do this, a modified nominal group technique consensus exercise will be undertaken. This will take place over half a day, adjacent to the annual ACPGBI. It will be opened to around 40 colorectal surgeons and around 15 patients from across the UK.

6.2 Study Design and statistical analysis

Observational cohort (n=800). Nested mixed method case-studies (n=20 patients). Discrete choice experiment (n=300 of cohort). Modified nominal group consensus exercise (n=40 surgeons, n=15 patients).

6.2.1 Consultant surgeon survey

6.2.1.1 Design and theoretical/conceptual framework

A paper and pencil survey will be undertaken by clinicians to identify the most frequently used interventions for specific clinical scenarios in current practice. The cover letter, which will be the email that is circulate to the surgical trainee network, highlights the rationale for the completion of the survey(25). This is a novel questionnaire that has been created following the CHERRIES statement (26) checklist of recommendations for use in this study.

6.2.1.1 Data collection

A pilot study will determine the clinical sensibility of the survey, this will also give evidence for the test-retest and the interrater reliability of the questionnaire. The pilot test will be conducted with a quota convenience sample of consultant colorectal surgeons. Thereafter, once the amendments have been implemented data will be collected using the trainee surgeon network to distribute the questionnaire. The data taken via a paper and pencil survey in order to maximise completion rates (27) will include questions on the mean number of procedures annually, primary elective treatments, factors affecting choice of procedure, treatment choice for recurrent disease presentation and factors affecting the choice of procedure for the treatment of a recurrent disease.

6.2.1.2 Sampling

The questionnaire will be run through the UK surgical trainee research collaboratives, led jointly by the South Yorkshire Surgical Research Group (SYSuGR) and the North-West Research Collaborative (NWRC). Collaborators will be asked to deliver the questionnaire to consultant colorectal surgeons in their units. The first point of contact will be made through the National Research Collaborative email lists and electronic contact to local collaborative leads will be cascaded locally. The collaborators will be asked that they circulate the questionnaire locally to three consultants and thereafter return the completed questionnaires to the Research Electronic Data CaptureTM (REDCap) system that will be hosted by the CTRU. The questionnaires will be anonymised at the respondent level. Previous surveys emulating this distribution method have yielded response rates of above 70% (28). It is hoped that the analysable response rate for the completion of the survey will be at least 61% as this has been seen as a valid response rate in previous postal surveys (29). Although this survey is being emailed for dissemination with potential participants, the participants will complete a paper and pencil copy.

6.2.1.3 Data analysis

All, aspects of data management will be provided by the CTRU in accordance with their standard operating procedures. The data emanating from this survey will be captured and stored in the REDCap software.

6.2.2. Cohort study

6.2.2.1. Data collection

Data will be collected mainly by research nurses. Baseline data, taken face to face immediately after consent, will include patient demographics, social and occupation factors, hair and skin type and previous pilonidal surgery history. Pilonidal disease characteristics, recorded by the surgeon immediately post-op will include pit numbers, track numbers, length, unilateral/bilateral distribution, position, presence of pus and previous surgical scarring. These represent all factors used in existing classification systems;(2)(3)(4)(5)(6)(7) and additional factors from the international consensus on classification. Description of the intervention will include all excision and closure techniques used with a description of major steps taken and potential variants thereof. Use of anaesthetic (general, regional, local), period-operative antibiotics, planned post-operative wound care will also be recorded.

Where the participant has a mobile, a pain numeric rating scale score will be recorded by the patient on day 1 post surgery via text reminder. A trained research nurse will collect structured questionnaire data and a pain numeric rating scale by telephone at seven days and six months, but face-to-face at the routine clinic visit at 4-6 weeks post-operatively.

Hospital notes and patient self-report will be used to assess recurrence and complications at six months. Following the six-month assessment patients will be contacted with a one-off follow-up at the end of the study unless the participant withdraws consent to further follow up or dies before the study completes. Patients will be contacted via email and telephone with a questionnaire incorporating persistence of symptoms. Hospital and GP records will be used to ascertain A&E attendance, repeat/additional procedures and unresolved complications due to PD, and interactions with primary care (GP consultations for PD, practice or district nurse visits for dressings).

All aspects of data management, including data protection and archiving, will be provided by the CTRU in accordance with their own standard operating procedures. The study as with the previous survey with surgeons will use REDCap for the capture and storage of participant data. REDCap uses industry standard techniques to provide security, including password authentication and encryption. Access to REDcap is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. Project-specific procedures for data management will be detailed in a data management plan.

6.2.2.2 Record keeping

Data will be collected by consultants and a research nurses who will record the data on the CRF. A copy of the consent and patient information sheets will be kept in the participant's hospital case notes. Data will be recorded on the REDCap data capture system. Site Principal Investigators will be responsible for ensuring that data is accurate and that the CRF has been completed correctly or an explanatory comment is added.

Participant names and contact details (including email addresses) will be collected and entered on to the database. Access to these personal details will be restricted to users with appropriate privileges. All other data will only be identifiable by participant ID number, and no patient identifiable data will be transferred from the database to the statistician when data analysis occurs. Access to REDCap is controlled by usernames and encrypted passwords, and comprehensive privilege management ensures that users have access to only the data required to complete their tasks.

Participant confidentiality will be respected at all times and the principles of the UK Data Protection Act (DPA) will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. The CTRU will provide worksheets (shadow CRFs) to allow the site staff to check what is required for data collection. The worksheets do not need to be completed if alternative source documentation is provided. However, they must be completed for data points where source documentation is not collected elsewhere and where completed the worksheets must accurately reflect the database as they form part of the source data.

Study records will be stored for 25 years after the completion of the study before being destroyed.

6.2.2.3 Type of management

The frequency of each management type will be summarised in relation to key characteristics, in particular the number of pits, uni/bilateral disease and recurrent disease. The variation in treatment across sites will be visualised using funnel plots, both overall and standardised to the risk strata derived in ii) below(30). These summaries will be used to identify areas of equipoise and front-running management strategies whose outcomes will be evaluated in the comparative analyses.

6.2.2.4. Risk stratification

Risk scores will be calculated based on existing rules and their respective prognostic abilities will be compared by assessing the relationship of each to patient-reported pain, incidence of complications and incidence of treatment failure requiring further intervention. The prognostic ability of the models will be assessed both overall and within subgroups of the most common treatment types. Exploratory modelling will assess whether use of additional covariates might help add to the predictive ability of existing models in this cohort.

6.2.2.5. Comparative outcomes

Analyses will be combined to assess the comparative outcomes of management options among the subset of patients for whom more than one treatment option was considered. For each two-way comparison, patients will be included if both treatment options were considered. The percentage of patients to whom each treatment was given will be reported, along with the pre-treatment risk scores in each treatment pathway. Two approaches will be used to adjust for potential differences in case mix: 1) stratification by severity of disease, and 2) propensity score matching. The average treatment effect among the treated (ATET) will be used to compare outcomes on each treatment to the hypothetical outcome on its competitor if sufficient overlap in the risk scores across the two treatments; no treatment comparisons will be undertaken unless sufficient overlap exists. Outcomes will be post-procedure pain, health utility and surgical complications. All analyses will be conducted using validated statistical software.

6.2.3 Mixed methods substudy

6.2.3.1 Design and theoretical/conceptual framework

This pragmatic concurrent mixed-method study will use a multiple-case design(31), nested in the observational cohort with two embedded units of analysis – longitudinal semi-structured interviews at baseline and six months, and quantitative cohort data to get an overview of patient views and experiences and, to assess which interventions patients would rather avoid and which

outcomes they most value. Topic guides will be based on aspects of the Coping in Deliberation (CODE) framework(24) and Sekhon's acceptability framework(32).

6.2.3.2. Sampling

We will sample at least 20 cohort participants for maximum variation(33) based on their pit characteristics and treatment. Consent to be interviewed will be sought by the researchers named on the delegation log at the same time as cohort consent, but will not be a pre-condition of the cohort entry. Spontaneously offered reasons for non-participation will be recorded.

6.2.3.3. Data collection

For the participants' comfort and convenience, we will collect data by telephone or Skype. To assess which outcomes are most valued by patients, and whether there are particular interventions they would rather avoid, the baseline interview guide will adapt key 'choice' (e.g. "did you let the surgeon choose your treatment?") and 'options' (e.g. "did the surgeon talk you through the risks and benefits?") questions from the CODE framework(24) At six months, the topic guide will ask CODE questions related to decision 'consolidation' (e.g. "Was this the right decision?"). At each time point-probing questions will be used to ensure coverage of relevant generic dimensions of acceptability(10) and to identify important attributes of interventions and levels of value they might place on those attributes, to inform the discrete choice experiment (Section 10). Interviews will last 30-40 minutes at baseline and 10 minutes at six months. All interviews will be recorded on encrypted digital recorders and fully transcribed. A minimum of 20 interviews should be adequate to understand common perceptions and experiences of people who make treatment choices for pilonidal disease, thereby achieving thematic saturation.(34)(35). We will continue to recruit either until we have reached data saturation, prospectively defined as six interviews since the last new theme arose (minimum n=12), or until we recruit a maximum of 25 individuals.

6.2.3.4. Data analysis

Two researchers will undertake all stages of the National Centre for Social Research 'Framework' analysis approach.(36) Familiarisation; identifying a thematic framework; indexing; charting; and, mapping and interpretation. They will independently code a sample of the transcripts, before conferring with each other and the patient panel (see Section 10) to confirm the working coding tree. Staff at the University of Sheffield CTRU will transcribe the interview data. They will sign a confidentiality agreement before they are given the audio to transcribe. Themes of *a priori* interest will relate to the conceptual frameworks and the requirements of the discrete choice experiment (Section 6.3.3). Analysis of participant themes

will take place in the latest version of NVivo (QSR International). We will employ a number of analytic integration strategies. A modified triangulation protocol(37) will be used to: (1) understand how disease characteristics and surgeon preferences interact with patient values in treatment choices; and, (2) to understand how participants appraise treatments given particular outcomes. We will use cross-walked themes and variables(38) in cross-case comparison joint displays(39) to look for convergence between cohort data (disease features / treatment choices / outcomes) with experiences, views and values. We will invite telephone / Skype / e-mail feedback on a lay summary of triangulated results from interviewees (member checking) and the final report will highlight the interpretations of our patient panel, the project management committee and the project steering committee (see Section 7) – both of which will include other patient experts.

6.2.4. Discrete Choice Experiment

6.2.4.1. Design and theoretical/conceptual framework

Discrete choice experiments (DCE) are an attribute-based measure of benefit, based on the assumption that health-care interventions, services or policies can be described by their attributes.(40)(41). In DCE's, respondents make decisions about quantity or quality differentiated versions of a good or service that requires them to make trade-offs. The resulting choices are analysed to estimate the overall utility (value) and willingness to trade between services. In the last decade, DCE's have increasingly been used to identify patient preferences in health and healthcare(40)(42)(43)(44). Accurate quantification of patient preferences for potential risks and benefits is crucial where no clear correct decision exists. Application of this method to pilonidal disease has not yet been undertaken.

6.2.4.2. Sampling

Clear guidelines are lacking in the literature on methods to calculate sample sizes, which vary substantially from 100 to 600(43)(30). We will adopt the formula used by Orme(45) to estimate the sample size necessary to achieve a tolerable margin of error (M.O.E.) – we estimate that this would be around 300 responses from our population, allowing for a 10% margin of error.

6.2.4.3. Development and design of choice questionnaire

During the first stage of the qualitative case study (Section 9) we will conduct semi-structured interviews to identify key attributes and levels important to patients. Data collection will continue until data saturation occurs – this is expected to be reached before 30 interviews, and may occur as soon as 12 interviews(34). Patient co-applicants will review the findings and they will be asked to comment on its comprehensiveness, treatment preferences, and to check that

outcomes have not been omitted. Data will be analysed using framework analysis(36) (detailed outline in section 9) in the latest version of NVivo (OSR International).

Discussions with clinical and patient experts will be conducted to confirm the list of attributes and levels. We will design choice profiles and pilot the choice experiment questionnaire with a random selection of patients and public involvement (PPI) members. They will be invited to participate in a pilot exercise to provide feedback on comprehension, interpretation and complexity of the choice questionnaire and to confirm plausibility of attribute combinations and levels. After we have validated the attributes and levels chosen, we will construct a choice experiment using NGene software (ChoiceMetrics, Australia). A main effects fractional factorial design will be used to avoid presenting too many alternatives to patients(44). We will present forced unlabelled choices “option 1” or “option 2” to respondents avoiding the use of an “opt out” alternative for the purposes of realism.

6.2.4.4. Data collection

Consented patients will be sent a link to their email addresses via Qualtrics, containing a participant information sheet and simple instructions on how to complete the choice questionnaire. The questionnaire will contain hypothetical choice scenarios (typically range from 8-12 choice sets to avoid cognitive burden) and will ask patients to make choices between two combinations of outcomes with varying levels. The questionnaire should take no more than 15 minutes to complete. Demographic data will be extracted from the cohort database, minimising participant burden.

6.2.4.5 Data analysis

Responses from the choice questionnaires will be modelled using a conditional logit model which is commonly used for the analysis of choice data(42). Regression coefficients will be used to estimate the relative importance of attributes and the marginal rates of substitution will be calculated (i.e., trade off preferences for outcomes)(42). Furthermore, latent class models will be used to analyse individual heterogeneity and to identify subsets of patients with varying preferences.

6.2.5. Consensus exercise: front running interventions

6.2.5.1 Overview

A modified Nominal Group Technique(46) consensus exercise will be undertaken with clinicians to identify front running interventions for specific clinical scenarios. This will be run at the ACPGBI Annual Conference 2021. Anonymised data from the cohort study will be made available to inform discussion, as suggested by the IDEAL collaboration(47). This session will

be used to propose comparators for specific clinical presentations, and validated by patients.

6.2.5.2 Participants

Applications for participation will be sought from consultant level members. The application list will be reviewed and around 40 surgeons will be invited to participate in the exercise. Participants will be selected to ensure wide geographic representation and mix of specialism and techniques offered in the treatment of PD, and the number of participants is high to reflect this.

6.2.5.3. Setting out the problem

Participants will be split into sub groups of 8-10, depending on attendance on the day. Each sub-group will be tasked with proposing a list of procedures, which might be used in a specific clinical scenario. Scenarios will be based upon common disease phenotypes seen in the cohort study. Each sub-group will have a facilitator. The facilitator will commence the session by outlining the clinical scenario to the group.

6.2.5.4. Idea Generation & Discussion

The sub-group will be allowed two-minutes to silently generate a list of ideas of procedures that might be offered in the scenario. Each participant will then share one item from their list, continuing around the group until no new items are proposed. Items will be documented on a flip chart, or on a computer screen visible to the group. The group will then discuss the proposed procedures, combining equivalent ideas where appropriate.

6.2.5.5. Round Robin Voting

The procedures proposed by each sub-group for each scenario will then be presented to the whole group, and ranked according to preference. The top 5 procedures for each scenario will be discussed by the whole group, followed by a second round of voting to identify the top three 'front running' procedures for each scenario.

6.2.5.6. Patient Validation of Proposed Trial Comparators

Patients/public representatives (n=15) will be invited to participate through social media and posters in participating hospitals. These participants will attend a session separate to, but in parallel to the idea generation phase outlined above. This session will involve sharing of patient preferences & experience from the discrete choice experiment and qualitative work, what the different surgical procedures are, and how they address the preferences. Time will be allowed for discussion and clarification of understanding.

Lay participants will then join the surgeon session, where the proposed comparators for each clinical scenario will be presented. Lay participants will rate each proposed comparison for relevance and acceptability using a 5-point Likert scale

The end product of this session will provide a list of surgeon-proposed front-running interventions for each clinical scenario, and a list of comparators for future trials. A similar strategy has been used in the past and generated generalisable findings(48).

6.3 Shared decision making and decision regret scale

In order to test how much patients were involved in the decision making process we will ask participants to complete a 5-point anchor collaboRATE questionnaire. Participants will also be required to complete a Decision Regret questionnaire 6 months after surgery. Data will be analysed to assess the degree of shared decision making at the time of surgery and whether there is correlation with the degree of shared decision making and the decision regret after surgery to assess the influence of various outcome measures and further define what is important to patients. This will be assessed in conjunction with the qualitative data collected.

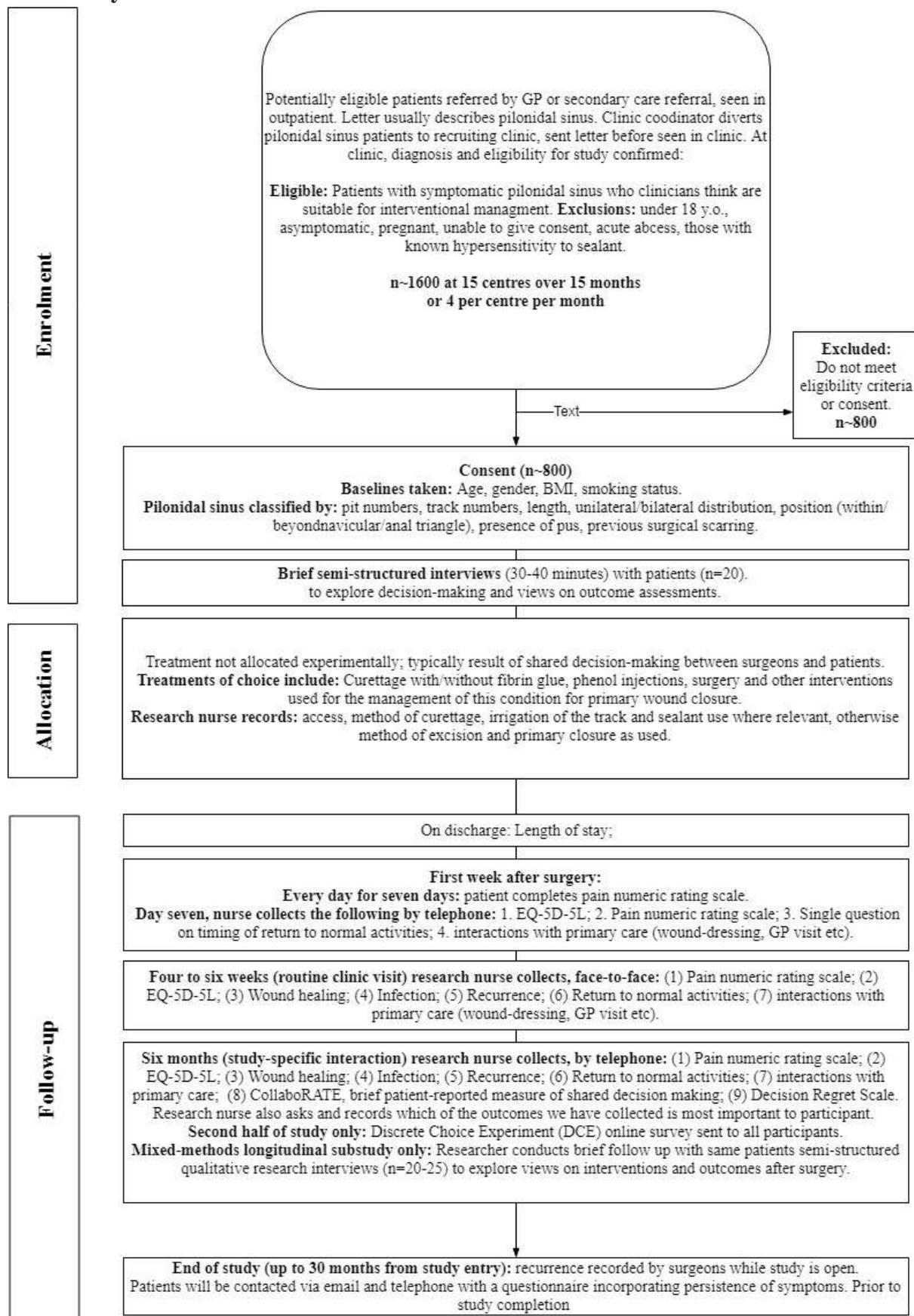
6.4 Outcome Measures

6.4.1 Primary and secondary outcomes

As this is a cohort study examining current practice there are no primary outcome measures per se. Identifying appropriate outcome measures for future studies is one of the objectives of the project. We aim to collect the following data.

1. Pain (numeric rating scale) on day 1 and day 7 post-operatively and at each follow up.
2. EQ-5D-5L quality of life score at each follow up(49).
3. Interactions with primary and secondary care
4. Length of time to healing
5. Return to normal activities
6. Complications
7. Recurrence

6.4.2 Study Flow Chart



6.4.3 Project Setting

Sheffield Teaching Hospitals NHS Foundation Trust (STH) will be the ‘clinical co-ordinating centre’ and house the Chief Investigator. A further 14 centres will be approached to recruit patients and deliver the trial. Coordination of the trial will be by the CTRU. Recruitment will take place in outpatients, surgery will take place in theatre.

6.5 Participants

6.5.1 Eligibility

The target population will be patients aged >16 years referred to collaborating centres for definitive elective surgical treatment of pilonidal sinus disease.

Inclusion criteria:

- Consenting patients over >16 years with pilonidal sinus disease.

Exclusion criteria:

- asymptomatic
- pregnant
- unable to give consent
- acute abscess
- hypersensitivity to the sealants

6.5.2 Proposed sample size

The study will open to all patients undergoing treatment for PD during the study period. We anticipate approximately 800 patients will agree to follow-up, with at least 100 within each of the front running management strategies. This will allow us to estimate proportions within each management strategy to a standard error of $\leq 5\%$ and pain numeric rating scale to within a standard error of 0.2 points of a 10-point scale, the latter assuming a standard deviation of 2 units.

6.6 Recruitment

6.6.1 Setting / Context

Patients will be enrolled between May 2019 and May 2020 from 15 UK NHS centres and whose Research & Development (R&D) departments have satisfied the team that they agree to the cost-structure of the study and who have demonstrated that they have a satisfactory throughput of potentially eligible patients. Management options (see Section 6.7) will reflect routine clinical care and will not be influenced by participation in this observational study. All

patients will be followed up for six months with a final, one-off follow-up at the end of the study.

6.6.2 Expected throughput of eligible patients

We currently have agreements in principle and principal investigators identified at all 15 NHS Trusts (see Section 8), to recruit 60 participants per centre over a 15-month period (an eventual steady state of 4.2 participants consenting per centre per month). The overall, study-wide recruitment for this Study is competitive with a maximum figure of 800 Participants. Once this target has been reached, the Sponsor will notify the Participating Site. No additional per Participant payments will be made by the Sponsor to the Participating Site for patients consented after such notification becomes effective, however we hope sites to aim to achieve a recruitment target of 60 participants each. The above projection is based on audit data obtained from various sources. HES data suggests over 13000 hospital admissions for pilonidal surgery occurred in 2011-12(10). Assuming about 150 hospital Trusts in England this equates to about 80-90 patients per Trust that undergo surgery for pilonidal disease per year or 100-110 over 15 months. A recruitment target of 60 patients during this period represents just over 50% of the total available population. An audit at Sheffield Teaching Hospitals (population served 500,000) confirms that around 50 patients with pilonidal disease undergo elective pilonidal surgery every 6 months (around 8 patients per month or 125 patients over 15 months). A recruitment target of 60 patients during this period represents less than 50% of the total available population. We have selected participating centres and co-applicants to include those that have a high volume pilonidal surgical practice (Cambridge, Derby, Portsmouth, Sheffield). Canvassing co-applicants and other principal investigators regarding their individual units suggests this target is achievable and sustainable on each site, with sufficient research nursing resource.

6.6.3 Feasibility Phase

Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocols based on the following recruitment criteria: Pilot study aims to recruit n=317 in 6m (green light); success criterion – recruitment of $n \geq 212$ in 6m (amber light). Recruiting fewer than 212 participants will be considered a red light.

6.6.4 Participant withdrawal and study completion

Participants may withdraw their consent to further follow-up at any point without giving a reason; this will not affect their care. All details will be recorded on the electronic

CRF. Outstanding data queries at study completion will be followed up as thoroughly as possible.

6.7 Intervention

Pit excision	Pit closure (options may be combined)
- Minimal (pit excision)	- No closure
- Major (take the whole sinus out)	- Midline
- Curettage (scraping out)	- Lateral
- Phenol injection/endoscopic ablation to obliterate track	- Flap
	- Glue

Although 18 excision-closure combinations are theoretically possible, published surveys suggest around six procedures are in common use (50)(51)(52)(53)(54). Among these procedures are major excision and leave open or midline closure, Bascom ‘pit picking’ (minimal excision), Bascom cleft closure (major excision and lateral closure), Karydakis (major excision and lateral closure), and Rhombic flaps (major excision and lateral closure). Selection is likely to be associated with disease characteristics and this will be assessed as part of the cohort study.

6.8 Safety Assessments

We will collect data on the Adverse Events (AEs) which are considered related to the study treatment including but not limited to those listed below as expected events on the CRFs. Any complications that occur following the intervention will be identified on the ‘Procedure details’ CRF and any further complications will be identified at the six-week clinic visit and at the six-month follow-up. Where these related events become Serious Adverse Events (SAEs) they

will be reported in accordance with the CTRU's and the sponsor's Standard Operating Procedures (SOPs). Unrelated AEs and SAEs will not be recorded. Site staff will be responsible for reporting all related SAEs; on identification they will complete an SAE form and send it to the CTRU and ensure that the local Principal Investigator has been informed. SAEs which are related and unexpected will be reported to the sponsor and we will expedite these to the Research Ethics Committee (REC) within 15 days of becoming aware.

6.8.1 Possible Expected Outcomes

The most common harms after surgery include, bleeding, haematoma, dehiscence of wound, maceration, and, flap oedema and necrosis. Dehiscence of wound (disruption of suture line leading to distraction of opposing wound edges), which can be partial length (a small section of the wound), or full length (full length of wound), and may affect only superficial layers (i.e. skin) or all layers. Maceration is defined as softening and breaking down of skin resulting from prolonged exposure to moisture.

6.8.2 Side effects and complications of anaesthetic

Common (affecting less than 1 in 10 patients) side effects from anaesthetic include feeling sick and vomiting, sore throat, dizziness, blurred vision, headaches, bladder problems, minor damage to lips or tongue, itching, aches and pains, pain during injection for drugs, bruising and soreness, confusion and memory loss. Uncommon (affecting less than 1 in 100 patients) side effects from anaesthetic include chest infection, muscle pains, slow breathing, damage to teeth, an existing medical condition getting worse. Rare or very rare (affecting less than 1 in 1000 or 1 in 10,000 people) complications are damage to the eyes, heart attack or stroke, serious allergy to drugs, nerve damage, equipment failure. Deaths caused by anaesthesia are very rare. There are probably about five deaths for every million anaesthetics in the UK.

Details of any of the AEs listed above will be recorded on the case report forms and participant completed questionnaires and reported periodically to the Sponsor and the Project Steering Committee (PSC).

6.9 Outcome Assessment Instruments

1. EQ-5D-5L quality of life score [The EuroQoL group] (49)
2. Pain numeric rating scale
3. Need for further treatment questionnaire
4. Recurrence questionnaire

5. Patient complications questionnaire
6. CollaboRATE questionnaire(22)
7. Decision Regret scale(23)
8. Cardiff Wound Impact Questionnaire(55)

Table 1 – Use of assessment instruments during study.

	Baseline	Intervention	Day 1	Day 7	Clinic visit (4-6 w)	6 mths	End of study
Baseline and other covariates							
Demographics	○	-	-	-	-	-	-
Pilonidal disease characteristics	○	-	-	-	-	-	-
Description of intervention (incl. anaesthetic, antibiotics, post-op care)	-	○	-	-	-	-	-
Length of stay	-	○	-	-	-	-	-
Patient-reported outcomes							
Pain numeric rating scale	○	-	●	●	○	●	-
Health state utility (EQ-5D-5L)	○	-	-	●	○	●	-
Return to normal activities	○	-	-	●	○	●	-
Interactions with primary care	-	-	-	●	○	●	-
Wound healing (single question)	-	-	-	-	○	●	-
Infection	-	-	-	-	○	●	-
Recurrence	-	-	-	-	○	● *	● *
CollaboRATE questionnaire	●	-	-	-	-	●	-
Decision Regret Scale	-	-	-	-	-	●	-
Cardiff Wound Impact Questionnaire	-	-	-	-	○	●	-

Harms							
Surgical	-	-	●	●	○	●*	●*
Qualitative outcomes							
Participant interviews (n=20-25)	○	-	-	-	-	●	-
Discrete choice experiment							
DCE e-mail	-	-	-	-	-	●	-

Key: ○ - assessment in clinic or theatre; ● - telephone / postal / electronic self-report assessment; * supplemented by hospital / GP notes.

6.10 Quality Control & Assurance

The study will be registered with the local R&D department of each centre and Sheffield Teaching Hospitals Trust will act as the sponsor for the Trial. Two committees will be established to govern the conduct of this study:

- the Project Steering Committee (PSC);
- Project Management Group (PMG).

These committees will function in accordance with Sheffield CTRU SOPs. As a minimum, the PSC will consist of a neutral chair with clinical and research expertise in colorectal surgery, a statistician and a patient representative. The Committee will meet every 6 months from the start of the trial. The PMG will comprise of a Trial Manager who will be jointly supervised by the Chief Investigator (CI) and the Assistant Director of the Sheffield CTRU and will liaise with the whole study team. The Trial manager will contact the CI and meet with the Assistant Director of the CTRU regularly.

Project monitoring procedures and site monitoring will be undertaken at a level appropriate to a risk assessment performed by the sponsor or their delegate.

7. Project Management

The project will be conducted in accordance with the UK Policy Framework for Health and Social Care Research. Sheffield Teaching Hospitals Clinical Research & Innovation Office who will act as the sponsor and may audit the study. A site agreement between the Sponsor, the CTRU and participating sites will outline responsibilities of all parties and be signed prior to commencement of recruitment at sites. All clinicians and research nurses responsible for

recruiting patients to the project will be required to complete training in GCP. Two committees will govern the conduct of this study and will function in accordance with Sheffield CTRU standard operating procedures. The Project Steering Committee (PSC) will consist of an independent chair and other professionals with relevant clinical and academic experience and two patient representatives. The PSC will meet every 6 months from the start of the project will review unintended effects of project conduct. The CI will chair monthly meetings of the Project Management Group (PMG) at which the day-to-day implementation of the study will be discussed. The Project Manager will be jointly supervised by the CI (SB) and the Assistant Director of Sheffield CTRU (DH), meeting by Skype at weekly intervals, and will liaise with the whole study team. Central monitoring will be undertaken at a level appropriate to a risk assessment performed by the sponsor or their delegate.

8. Ethical Issues

The ethical issues in this trial will be related to the identification and recruitment of patients, the procedure for gaining fully informed consent, and data protection arrangements.

The trial documentation, including this protocol, will be submitted to a local REC. The patient information leaflet, patient consent form, and any other patient facing documentation are included in the ethics application.

The trial will be submitted for local NHS research governance approval for each participating trust.

The management of symptomatic pilonidal disease is generally dictated by a combination of patient choice, surgeon's preference and local expertise, experience and facilities. There are various treatments available that are considered standard practice for this group of patients.

9. Patient and public involvement

9.1 Aims

We aim to make study participation attractive and procedures acceptable to eligible patients and outputs useful to the wider patient population. PPI will guide planning in the set-up period, inform responses to challenges in the accrual period, and support development of the plain language and scientific summaries for dissemination.

9.2 Description of the patients and carers to be involved

This study has been developed in consultation and collaboration with patients from multiple UK sites who suffer from pilonidal disease. Three of these expert patients, who have had

experience of different management approaches to their disease, are included as co-applicants (Section 18).

9.3 Methods of involvement

We will convene a patient panel who will meet on a quarterly basis to instruct the project team (represented by the study manager and CI), with two or more expert representatives attending PMG meetings in between. Patient representatives not on the project team will also be invited to join the PSC. Expert patients sit on the study management committee, representing patient concerns and inputting into the study conduct and analysis. These or other patient representatives will also work with the mixed-methods research team to assist in the design of the research interviews, associated information materials, and in the subsequent interpretation of emerging findings. The patient reference group is of central importance to the mixed-methods research component, which aims to understand how patient values inform the trade-off between surgery and the risk of recurrent disease (Section 6.2.2). Patient experts will also be core in supporting other patients in the selection outcome measures for any future trial (Section 6.3.4). PPI representatives will be invited to contribute during the write-up period to ensure the needs of a service-user audience are met. The lay summary of the findings will be written by our expert patients, with support from members of the PMG. Training and mentorship will be provided by Sheffield Teaching Hospitals and the School of Health and Related Research for patient experts involved in research activities. All PPI involvement will be reimbursed according to the INVOLVE guidelines.

10. Methods of Dissemination of Results

Our strategy for making the outputs of this research have real NHS impact relies on involving key stakeholder groups with the task of dissemination and knowledge transfer (KT). Our KT goals are: change/confirm current policy and practice through the Royal Colleges/NICE and other individual organisations; and, give patients a greater understand of the options available to them and the trade-offs involved.

The findings of our research will be made available to the clinical community through publication in high “impact”, peer reviewed journals. We will present at national and international conferences to clinicians who are involved in the care of surgical patients. Our multidisciplinary team of nationally renowned clinicians will ensure effective communication of study findings to a wide range of specialist audiences capable of adopting change at their local level. International audiences will be targeted through the European Society of Coloproctology and the Pilonidal Sinus Society through our collaborator, Peter Wysocki

(President of the Society). We will provide specific reports on study findings for healthcare policy makers. With the support of the Trial advisory group, we will ensure that key research evidence is made available to the Department of Health, Royal College of Surgeons, NHS Trusts and other stakeholders. If funded, formal adoption of the study by the Association of Coloproctology of Great Britain and Ireland (ACPGBI) will be sought. The ACPGBI promotes and fosters the care of patients with bowel related disease, which includes pilonidal disease. Adoption would provide the study with a conduit of dissemination and the regular news emails from its affiliated Societies and Charities reaching all members with an interest in surgery currently numbering well over 1000 UK clinicians. These are key physicians charged with implementing many of the surgical components of the intervention under scrutiny and adoption of the recommendations generated by the proposed research would be vital for its success. We will advise NICE on the implications of our findings, if any, and recommend a pathway for optimal implementation.

In partnership with our participating hospitals and PPI representatives, our findings will be made available to front line NHS staff, across all care disciplines. Open access publication will ensure implications of our research findings are rapidly and widely available. We use plain language summaries to communicate findings to the public over a range of media platforms, for example publishing a summary video on popular media streaming sites such as YouTube, engaging in radio interviews and submitting press releases. We will also undertake the more dynamic methods of integrated knowledge transfer through engagement of our PPI members over the course of the study, two of whom are co-applicants. Our representatives have the capacity to act as ambassadors for the study and will have the opportunity to transfer knowledge on to peers in other PPI forums and also on to the wider public over the course of the study.

11. Costing the project

11.1 Service support costs (research nurses)

It is estimated that research nurses will be required for 1.5 hr per patient for 2 face to face & 2 phone visits.

11.2 Treatment costs (cost of the procedures)

As this is a cohort study assessing current standard practice, there are no additional treatment costs.

12. Funding Source

This trial is funded by the National Institute for Health Research NIHR Health Technology Assessment (HTA) programme (project number or ref 17/17/02).

13. Department of Health and Social Care disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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Protocol amendments since initial REC approval

Version number	Changes made	Date of REC approval	Amendment number