The ORION Trial

RadiO fRequency ablatION for haemorrhoids

A Pragmatic multicentre patient-/ assessor-blind parallel-group individual participant randomised (1:1 allocation) randomised controlled trial with economic evaluation.

STATISTICAL ANALYSIS PLAN
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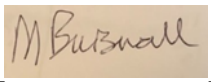


_____ _____ _18__/04_/_23__

Dr Matthew Bursnall Date

Statistician, Sheffield CTRU

Approved by

_____ __18__/04_/_23__

Mike Bradburn Date

Senior Statistician, Sheffield ScHARR

____ _____ _20__/__4_/__23___

Prof Steven Brown Date

Chief Investigator, Consultant surgeon, Northern General Hospital

__ _____ _17__/__04_/__23___

Ruth Knight, Date

DMEC Statistician, Statistician, University of Liverpool

_____ _16__/04___/_23____

Jeff Garner, Date

TSC Chair, Consultant surgeon, Rotherham NHS Foundation Trust

Abbreviations

AE	Adverse Event
CI	Chief Investigator
CCC	Confirmation of Capacity and Capability
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
GA	General Anaesthetic
GCP	Good Clinical Practice
HAL	Haemorrhoidal Artery Ligation
ICC	Intraclass Correlation Coefficient
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LA	Local Anaesthetic
MCID	Minimal Clinical Importance Difference
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QALYs	Quality Adjusted Life Years
RFA	Radio Frequency Ablation
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SOPC	Surgical Out Patient Clinic
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

Trial Summary

Trial title	The ORION Trial: RadiO fRequency ablation for haemorrhoids

Trial start date	01/07/2021
Trial end date	31/01/2025
Trial design	A pragmatic multicentre patient-/ assessor-blind randomised (1:1 allocation) controlled trial with internal pilot and economic evaluation .
Research Question	For haemorrhoids that are considered appropriate for surgery, is radiofrequency ablation superior in reducing post-operative pain and have recurrence no worse than current recommended interventions?
IMP	Radiofrequency ablation
Comparator	Surgeon's choice of current recommended surgery
Trial participants and setting	Patients aged 18 or over presenting in NHS Hospital trusts with symptomatic grade II or grade III haemorrhoids which the clinician has determined to be appropriate for a surgical intervention.
Outcomes	<u>Internal pilot</u> Red/amber/green Stop-go criteria based on participants recruited per-month per-site in a 6 months pilot and number of sites open. <u>Co-Primary outcomes</u> Recurrence at 12 months post procedure and pain at 7 days post procedure <u>Secondary outcomes</u> Pain score at 1 and 21 days, 6 weeks and 12 months post procedure; days of work lost; Persistence of symptoms at 6 weeks post procedure; Haemorrhoid severity score; EQ-5D-5L at 1,7 and 21 days, 6 weeks and 1 year post procedure; Vaizey incontinence score at 6 weeks and 1 year post procedure

Recruitment	01/03/2022 – 31/05/2023 (15 months)
Follow-up	01/03/2022 – 31/07/2024 (29 months)
Target sample size	376 participants (188 per arm)
Definition of end of trial	The end of the trial is defined as the date of the last recruited participants' 12-month follow up visit. Sites will be closed once data cleaning is completed and the regulatory authority and ethics committee will be informed.
End of study main analysis	Analyses will use generalised estimating equations (GEE) with a binomial family and logit link for recurrence at 12 months and an identity link for pain at 7 days; Grade of haemorrhoid (and baseline score for pain) as fixed effects and surgeon as a random effect.

1 Background and Trial Rationale

Haemorrhoids result from enlargement and pathological changes in the haemorrhoidal tissues in the anal canal. They can be painful and can disrupt personal and working lives

Treatment is dictated by the degree of symptoms and the degree of prolapse.

- Patients with no prolapse or prolapse on straining and spontaneous reduction may be treated successfully with less invasive outpatient procedures ("office therapies") but these can have a high recurrence rate.
- For those with more extensive prolapse or those where office treatment has failed, surgical intervention may be required, ranging from haemorrhoidal artery ligation through to stapled haemorrhoidopexy or haemorrhoidectomy (surgical excision). These require regional or general anaesthetic and are associated with post-operative discomfort, possible overnight hospital stays and delayed return to normal activity. All three are available on the NHS.
- An alternative procedure is radiofrequency ablation (RFA). As with current recommended surgical interventions, RFA is primarily intended for patients who failed to respond to "office treatments" and those with a higher degree of prolapse where office procedures are likely to be ineffective. It can be done under local anaesthetic but is usually done under general anaesthetic in the UK.

As RFA does not excise tissue or generate excessive heat, it should result in minimal discomfort and has been suggested to be faster than excisional treatments with a more rapid recovery and less expensive for the NHS compared to surgeon's choice of currently available options.

The evidence base for these claims is however limited and has not been subject to a randomised comparison.

2 Research question and objectives

2.1 Research Question

For haemorrhoids considered appropriate for surgery, is radiofrequency ablation superior in reducing pain at 7 days post-operation, and non-inferior in preventing recurrence at 12 months post-operation, and more cost effective compared to surgeon's choice of current recommended interventions available on the NHS?

2.2 Objectives

1. An internal pilot to determine the feasibility of recruiting to a full-scale trial (see section 10).
2. A full-scale trial to compare, for people with haemorrhoids considered appropriate for surgery, the effectiveness and cost effectiveness of radiofrequency ablation compared to surgeon's choice of surgery based on the hypotheses in section 4.2.

3 Outcomes

3.1 Feasibility outcomes

The Trial Steering Committee will assess the feasibility of the trial against the following outcomes

- Number of sites that have been open for six months
- Number of sites opened
- Participants recruited per site per month over the first 6 months

3.2 Main Trial Outcomes

3.2.1 Co-Primary outcomes

- Recurrence at 12 months post procedure
- Numeric Pain Rating Scale (NPRS) at 7 days post procedure

3.2.2 Secondary outcomes/endpoints

- NPRS (1 and 21 days, 6 weeks and 12 months post procedure)
- Number of days of work lost (measured by research nurse at 6 weeks post procedure)
- Persistence of symptoms at 6 weeks post procedure
- Haemorrhoid severity score [12] (1 and 21 days, 6 weeks and 12 months post procedure)
- EQ-5D-5L [13] (day 1, day 7, day 21, 6 weeks, 1 year post procedure)
- Self-report, 7-item Vaizey incontinence score (6 weeks, 1 year post procedure) [14]
- Health and social care resource use questionnaire (6 weeks, 1 year post procedure) • Complications (reported during procedure, at 6 weeks and at 12 months]
- Cost.
- Recurrence based on the patient reported recurrence only (see 17.1) to provide additional information from the patients' perspective.

3.3 Safety Outcomes

The number of participants experiencing a) each outcome type below at least once and b) any of the outcome types below at least once at 3 time points (reported during procedure, at 6 weeks and at 12 months].

- Complications of anaesthesia
- Post-surgical complications
- Post-surgical complications leading to SAE (see 17.5 for definition).

This will include but not be limited to the AEs expected a-priori (see section 21 for list)

3.4 Outcomes beyond the scope of the SAP

Analysis of the following outcomes is covered in a separate Health Economics Analysis Plan (HEAP) and are not covered further in this SAP

- Health and social care resource use questionnaire
- Cost
- Cost benefit analysis relating EQ-5D-5L to cost (although EQ-5D-5L will be converted to index values and compared between arms using formal statistical tests).
- Cost benefit analysis relating any other outcomes to cost

4 Design

4.1 Design overview

ORION is a pragmatic multicentre patient-/ assessor-blind parallel-group individual participant randomised (1:1 allocation) controlled trial combing a non-inferiority design for recurrence and a superiority design for post-operative pain. RFA will need to demonstrate significance for both endpoints to be considered superior.

4.2 Hypotheses for co-primary outcomes

4.2.1 Non-inferiority design for recurrence

H_0: $P_{RFA} - P_{SC} \geq \Delta$ v. H_1: $P_{RFA} - P_{SC} < \Delta$; where P_{RFA} is recurrence rate in the RFA population, P_{SC} is recurrence rate in the surgeon's choice population, Δ is the non-inferiority limit and higher recurrence indicates a less successful procedure. This one-sided hypothesis will be tested at the 2.5% significance level. The non-inferiority limit is set at Δ = 10%.

4.2.2 Superiority design for post-operative pain

H_0: $\mu_{RFA} = \mu_{SC}$ v. H_1: $\mu_{RFA} \neq \mu_{SC}$, where μ_{RFA} and μ_{SC} are mean NPRS pain scores at 7 days post treatment for the RFA and Surgeon's choice populations respectively. This two-sided hypothesis will be tested at the 5% significance level. Lower NPRS scores indicate less pain. The minimum clinically important difference is set at -0.6 pain score units (1/3 standard deviations).

4.3 Sample size

The target sample size is 376 participants (188 per arm) and is based on two co-primary endpoints: i) a non -inferiority design for recurrence and ii) superiority design for pain at 7 days.

Previous research has demonstrated RFA is associated with a recurrence rate between 4% and 15% compared with 15% for haemorrhoidectomy and 25%-30% for HAL. Our PPI members have advised us that RFA would be acceptable if we could rule out a 10% increase in recurrence, which we have used as our inferiority limit, accompanied by a reduction in pain. Our trial will recruit 376 participants (188 per arm), which provides 90% power to declare non-inferiority based on a 15% drop out, an Intra-class Correlation Coefficient (ICC) of 1% among 16 surgeons, a one-year recurrence rate of 15% for intervention and 20% for usual care, a non-inferiority limit of 10% and a one-sided 2.5% significance level. These assumptions are heavily based on our previous HubBLe trial [1], which found a 12% dropout in the HAL surgery arm and a zero ICC for 12-month recurrence. A sample size of 376 ensures a 90% power to detect a minimal clinical importance difference (MCID) of 0.6 points (1/3rd of a standard deviation) in NPRS reported pain at 7 days at the two-sided 5% level assuming 5% missing data, a correlation of 0.5 between baseline and follow up and an ICC of 1%. No adjustment for multiple testing is necessary since RFA will need to demonstrate significance on both endpoints.

4.4 Randomisation

Once eligibility has been confirmed and baseline data recorded (see 9.3) participants will be centrally randomised, stratified by centre, using the CTRU online randomisation system (SCRAM) to RFA or surgeon's choice, in the ratio 1:1. The doctor or nurse will access the web-based randomisation system, patient details (ID, date of birth) will be entered and the treatment allocation will be returned.

4.5 Planned analysis

The feasibility outcomes relate to retention only and these will be reported and assessed descriptively after the feasibility pilot period with no formal statistical testing. There will be a single analysis of all other outcome at the end of the trial guided by this SAP.

5 Summary of Trial Implementation

5.1 Participant identification

A member of the patient's care team will identify and consent eligible participants that have been referred to collaborating centres for treatment of haemorrhoids.

5.2 Inclusion and exclusion criteria

5.2.1 Inclusion criteria

- Patients aged 18 or over with symptomatic grade II or grade III haemorrhoids

- And patients that have failed conservative managements (diet and lifestyle changes) and want further intervention
- And/or patients who have either failed one episode of RBL or have grade III haemorrhoids considered inappropriate for RBL treatment and/or have grade II or III haemorrhoids which the surgeon feels operative intervention is appropriate

5.2.2 Exclusion criteria

- Patients with known perianal sepsis, inflammatory bowel disease, anal or colorectal malignancy, pre-existing sphincter injury
- Patients with an immunodeficiency (HIV or other medical cause)
- Patients unable to have general or spinal anaesthetic
- Patients taking Warfarin, or direct oral anticoagulants that cannot be safely stopped prior to surgery, or that have any other hypocoagulability condition that may increase the risk of bleeding
- Patients who have a pacemaker fitted
- Patients who have already had surgery as part of the ORION trial
- Pregnant women
- Patients unable to give full informed consent

5.3 Summary of Trial treatments

In order to compare RFA with the currently available surgical treatments for haemorrhoids, patients will be randomised to receive either:

- Group A: RFA using the Rafaelo® device or
- Group B: Surgeons' choice of other procedures currently available on the NHS.

5.3.1 Radiofrequency ablation (RFA)

In the UK it is generally performed under general anaesthesia with the patient positioned in lithotomy but it can also be performed under local anaesthetic. The submucosa of haemorrhoidal tissue is infiltrated with approximately 1 ml of bupivacaine 0.25%. In addition to achieving local anaesthesia, this step creates a fluid barrier to prevent the transmission of heat to the internal anal sphincter muscle. A needle probe then applies radiofrequency energy to the haemorrhoidal cushion to restrict the haemorrhoids blood supply and cause it to necrose and fall away.

5.3.2 Currently available NHS treatments

There are broadly three options although each of them can also be done in slightly different ways (see protocol for details). As this is a pragmatic trial the control group will be 'surgeon's choice' of method using surgeons chosen approach. The three broad approaches are:

1. **Stapled haemorrhoidopexy** aims to correct haemorrhoidal prolapse by excising a ring of tissue above the haemorrhoidal cushions with immediate reanastomosis of the mucosa with the use of staples.
2. **Haemorrhoidal Artery Ligation (HAL)** Haemorrhoidal arteries feeding the haemorrhoidal cushions are detected and ligated using a suture or 'pexy' suture.
3. **Haemorrhoidectomy** Open or closed excision and excising of the haemorrhoidal cushions whilst preserving healthy intervening mucocutaneous bridges.

5.4 Blinding

The intention is for patients to be blinded to the operation they receive. This is generally feasible because usual practice in most sites is for the investigational and comparator procedures to be performed under general anesthetic (GA). As the HTA is a commissioner of pragmatic trials, clinicians will have leeway to perform the operation under local anesthetic (LA) and in this situation it is more likely that participants will become unblinded. Adequacy of blinding will be checked by asking participants at the 12-month follow up to guess which treatment they received.

Assessors (research nurse or clinician) will also be blinded to the intervention, as no inspection of the surgical site is required. The trial statistician(s) will remain blinded throughout the study, but will be unblinded at data-base freeze, for analysis. The Senior Statistician will be unblinded to the treatment allocation throughout the trial but will review and approve the statistical analysis plan version 1 before seeing any outcome data. In most sites patients will be blind to treatment allocation but in some sites they may be informed of the operation they are getting. Unblinding (planned or unplanned) will be recorded.

6 Assessment and data collection

6.1 Assessment

Assessment occurs at four phases

- Baseline (patient characteristics and baseline scores collected at SOPC on day of surgery)
- Short term outcomes (pain, EQ5D) using telephone surveys (day 1, 7 and 21 post-procedure)

- Outcomes at 6 weeks post procedure will be collected in clinic if the usual clinic is face to face or by telephone questionnaire
- Longer term outcomes (including recurrence) using telephone surveys (patients) postal surveys (GP, consultants) and clinical notes at around month 12 post-procedure

For further details see Figure 1, Table 1 and section 17.

6.2 Data collection and recording

Participant study data will be recorded on study-specific case report forms (CRFs) and patient questionnaires and then entered onto a remote web-based data capture system, transferring data to Sheffield CTRU for analysis. Project-specific procedures for data management will be detailed in a data management protocol.

6.3 Timing of assessment and acceptable reporting windows

Baseline measures will be made on the day of surgery with all future assessments anchored to this date. For clinically relevant windows associated with other follow-up assessments see section 17.3.

6.4 Participant discontinuation

6.4.1 Participant withdrawals

Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent. The numbers and percentages of withdrawals will be reported by arm, follow-up point and whether they withdrew from the intervention only or the trial.

6.4.2 Lost to follow-up

Participants will be defined as lost to follow up if they do not attend or contribute data at a particular visit and do not attend or contribute data at all subsequent follow-up points. . The numbers and percentages of loss to follow-up will be reported by arm and the first follow-up point for which they did not attend or contribute date.

6.4.3 Transitory missing from follow-up

Where participants do not return data at one follow-up but subsequently return data at one or more follow-up they will be reported as part of the missing data summary (see section 13) and shown separately to those lost to follow-up in the CONSORT diagram (see section 9.1).

Figure 1 Summary of participant flow

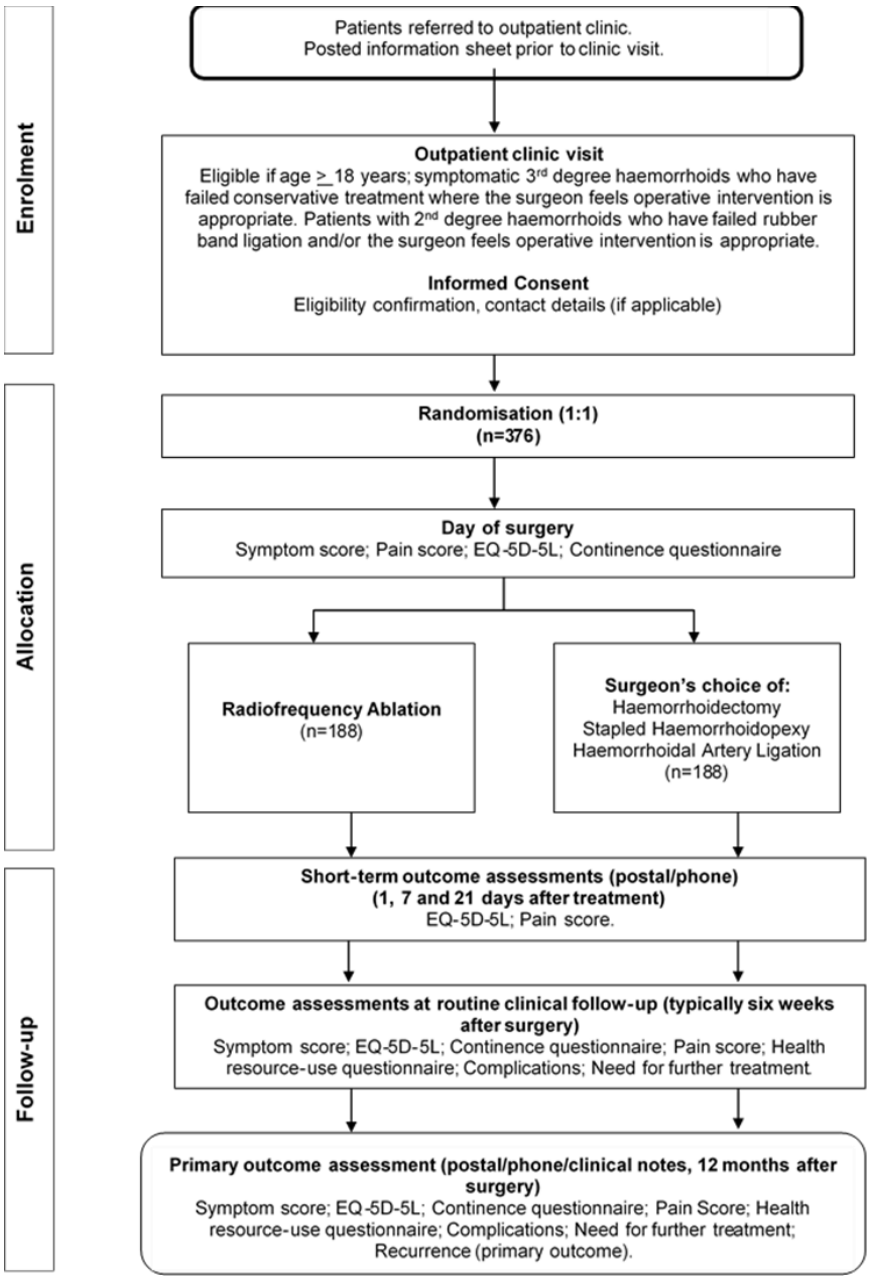


Table 1 Study assessments schedule

	Pre rand'n	Rand'n	Day of surgery	1 day post	7 days post	21 days post	6 weeks post	1 year post
EQ-5D-5L			c	T	T	T	cP	TP
Numeric Pain Rating Scale			c	T	T	T	cP	TP
Vaizey incontinence score			c				cP	TP
Haemorrhoids severity score			c				cP	TP
Randomisation		c						

Operation Details			c					
Complications review interview							cP	TP
Days of work lost							cP	
Health and social care resource use							cP	TP*
Need for further treatment questionnaire							cP	TP*
Recurrence (Primary outcome)							cP	TP*
Clinical appearance at proctoscopy (where applicable)							c	

*c= Surgical Outpatient clinic, T= telephone, P= postal survey, * = supplemented from case notes,*

6.5 Safety data collection

Adverse Events (AEs) and Serious adverse events (SAEs) considered unrelated to the study treatments are not being recorded. AEs and SAEs considered related to the study treatments and which 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 twelve-month follow-up.

7 Trial oversight

7.1 Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources and consider recommendations from the DMEC, including the recommendation of trial termination. The TSC will meet every six months from the start of the trial and consist of an independent chair and other professionals with relevant clinical and academic experience and two patient representatives.

7.2 Data Monitoring and Ethics Committee

The Data Monitoring Ethics Committee (DMEC) will consist of an independent statistician, and at least two independent physicians with clinical trial expertise. There will be no interim analyses (other than for the purposes of the blinded internal pilot) or definitive stopping guidelines, but the DMEC will be able to request unblinded data and recommend study termination to the TSC/funder on grounds of safety or futility. The DMEC will meet every six months from the start of the trial to review reports provided by the CTRU and assess the progress of the trial.

7.3 Trial Management Group

The Trial Management Group (TMG) is comprised of the CI, trial manager, statistician, data manager, health economist and grant co-applicants. PIs will also be invited to represent sites. The CI will chair monthly meetings with the TMG to discuss the day-to-day implementation of the study. The Trial Manager who will be jointly super-vised by the 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.

8 Analysis Populations

8.1 Safety Population

All participants who receive either the treatment or control condition procedure will be analysed as treated irrespective of allocation. We will exclude participants who received neither index procedure.

8.2 Analysis populations for end of trial analysis

8.2.1 Co-primary outcomes

Analysis populations for the co-primary outcomes are summarised in Table 2.

8.2.2 Secondary outcomes

For continuous secondary outcomes (see Section 15.1) we will use the primary population used for pain at 7 days as summarised in Table 2. For binary outcome (see Section 15.2) we will use the primary population used for recurrence at 12 months as summarised in Table 2.

Table 2 Analysis populations for end of trial analysis Population	Pain at 7 days	Recurrence at 12 months

Modified Intention to Treat (mITT)	Participants will be excluded if they • received neither index treatment - assumes they would also have declined treatment if allocated other arm – valid due to patients being blinding • patients with missing covariate or pain data (incl. withdrawals between procedure and 7 days where consent to use data withdrawn) – see 13.3 • patients without recorded consent information	Participants will be excluded if they • received neither index treatment - assumes they would also have declined treatment if allocated other arm – valid due to patients being blinding • patients with missing recurrence or covariate data (incl. withdrawals between procedure and 12 months where consent to use data withdrawn) • patients without recorded consent information • died for any reason – assumes the death was unrelated to the treatment or condition If there is switching from RFA to surgeon's choice this will be counted as treatment failure (recurrence) based on the assumption that this occurred on the operating table because the haemorrhoid was larger than envisioned from less invasive outpatient inspection (but still grade ii or iii and hence eligibility still met) and
		the surgeon decided they would rather use a tried and tested method from the surgeon's choice (control arm) list. If there is switching from surgeon's choice to RFA this will be include in the surgeon's choice arm based on the assumption that this was done in error because there is no medical reason for this switch.

Per protocol (PP)	Participants will be excluded if they • received neither index treatment • switched index treatment prior to procedure • have missing pain or covariate data • have no recorded consent information • Outcome data reported outside of the acceptable windows (see 17.4) • Deaths for any reason	Same as pain at 7 days
As treated (AT)	Participants will be excluded if they • received neither index treatment • have missing outcome or covariate data • have no recorded consent information • Died for any reason Participants who switched index treatment prior to procedure will be included in the treatment they received	Same as pain at 7 days
Intention to Treat (ITT)	Participants will only be excluded if they • have missing outcome or covariate data • have no recorded consent information	Same as pain at 7 days

Conservative	Same as the mITT population but also excluding participants who switched index treatment. This assumes all switching is from RFA to control on the operating table because the haemorrhoid is larger than envisioned from less invasive outpatient inspection (but still grade ii or iii and hence eligibility still met) and the surgeon decided they would rather use a tried and tested method from the surgeon's choice (control arm) list. This is a conservative assumption in favour of the control. However, the larger haemorrhoid means they are likely to be at the higher end of the pain distribution (all other things being equal) so this assumption may introduce unverifiable imbalance between arms.	Same as mITT above
Multiple Imputation (MI) for missing data	Multiple imputation using chained equations (MICE) (see section 13.4)	We will use simulation to assess how many of those with missing data would need to have a recurrence to change the conclusion reached about noninferiority (from established to notestablished and vice-versa as appropriate) – see section 13.5

8.3 Identification of inter-current events (ICEs)

We will identify these ICEs using the following data sources:

- Outcome data reported outside of the acceptable windows – date of follow-up completion, SAE or medical note (see section 17.3 for window details)
- Non-uptake of allocated procedure – reconciliation between randomisation schedule and details of procedure forms
- Switched to other arm– reconciliation between randomisation schedule and details of procedure forms
- Death – SAE form and discontinuation form
- patients without recorded consent information – consent form
- withdrawals – completion and discontinuation form
- missing pain or covariate data – individual follow up forms as appropriate

8.4 Purpose of analysis populations

For all populations and both co-primary outcomes the numbers and proportions excluded for each reason will be summarised by arm. Between-arm differences in exclusion rates will be summarised and assessed qualitatively for the potential to bias the treatment estimates.

Only the safety outcomes will be analysed using the safety population (see sections 3.3 and 16).

The primary analysis will use the Modified Intention to Treat (ITT) population based on complete cases (see 13.3). This will be used instead of the multiple imputation (MI) population because MI can provide an inaccurate adjustment for missing data or adjust in the "false" direction. Instead, we will interpret any bias stemming from missing data by looking at the results from all populations in the round. The greater the level of missingness, the more weight is likely to be given to the results from the multiple imputation population.

Sensitivity analysis using the per-protocol (PP), as treated (AT), conservative and Multiple Imputations (MI) populations (see section 8) will be for the co-primary outcomes only. There is no planned sensitivity analysis for secondary outcomes.

9 Participant flow, screening and baseline characteristics

9.1 Participant flow

Number of participants, numbers consented and their journey through the trial will be summarised in a standard parallel trial CONSORT diagram. Cluster sizes will be summarised by arm in a separate table.

9.2 Screening information

Baseline characteristics where available will be reported for all those screened and compared with those consented to assess representativeness.

Screened individuals will also be summarised by month and site; reason not eligible (see section 9.2) and reason not interested (not interested in intervention, unwilling to be randomised, not willing to complete outcome forms).

9.3 Baseline characteristics

We will present baseline summaries by treatment group and overall for the below using counts and percentages for categorical data and, for continuous data, mean/standard deviations or median / IQR depending on distributional form and min/max.

- Initial presentation (office / surgical)
- Age
- Sex
- Grade of haemorrhoid
- Has the participant failed conservative managements (diet and lifestyle changes)?
- Has the participant failed one episode of RBL?

- Does the participant have grade III haemorrhoids considered inappropriate for RBL treatment?
- Concomitant medication [Yes/No and list]
- Other significant conditions [Yes/No and list]
- Weight
- BMI
- Baseline score for all outcome scores

We will assess baseline data for comparability between groups. We will describe any notable difference and consider sensitivity analyses on the primary outcome but statistical testing will not be undertaken.

Data collection for concomitant medications and other significant conditions includes the use of free text boxes. Where responses use different terms for similar medication / conditions we will group these into appropriate categories in consultation with the CI. Counts for each of the free-text responses will also be provided after suppressing any identifying information in the free text.

10 Analysis of Feasibility Outcomes

10.1 General considerations

The original progression criteria are described in 10.2. These have now been revised by agreement with the funder and are subject to ongoing monitoring and revisions. If the result of the feasibility phase is to stop, the trial report will follow the updated CONSORT statement for pilot studies [2]. We will present summary statistics and confidence intervals but not perform hypotheses tests. Either way, the final feasibility outcomes agreed with the funder will be reported and assessed against descriptively in the final report.

10.2 Original feasibility outcomes

The projected date for assessment of the feasibility is August 2022, 6 months after the planned start of recruitment in March 2022.

There will be no formal hypothesis testing of feasibility outcomes. Data management will provide summaries of the recruitment outcomes in regular status reports and at the end of the feasibility stage for the Trial Steering Committee to assess the feasibility of the trial.

Feasibility will be assessed by the TSC against red/amber/green stop/go criteria with an emphasis on discussion about whether the trial is likely to meet its objectives on the current trajectory and, if not, whether modifications can made so it meets its objectives.

The following red/amber/green stop/go are based on target pilot recruitment of 124, with around 8 sites recruiting for 6 months.

- Green - go: 124 participants (100% of 6-month target; 41% of final 12- month target; 2.58 participants per site per month assuming 6 months recruitment in 8 pilot sites).
- Amber - funder discretion: 83-123 participants (67% to 99% of 6-month target; 27% to 40% of final target; between 1.7 and 2.56 per site per month in 8 sites).

- Red - stop: fewer than 82 participants (less than 67% of 6-month target; less than 27% of 6month target; less than 1.7 patients per site per month assuming 6 months recruitment in 8 pilot sites).

In addition, the aim is to have 15 sites open by the end of the 6 months pilot period.

As this is an internal pilot, clinical and patient-reported outcome data from the pilot / feasibility stage will be included in the final analysis and no differentiation made between participants recruited during the pilot and after its completion.

11 General analysis principles for end of trial analysis

For primary and secondary outcomes, we will check model residuals and, in case of major assumption deviations, we may fit additional models for sensitivity with statistical discretion.

All models will control for grade of haemorrhoid (fixed effect) and surgeon (random effect) and continuous outcomes will include baseline score as a fixed effect covariate. Stratification was based on centre/site but most sites only have one surgeon in the trial so we will adjust for surgeon using a random effect instead of site. We use surgeon instead of site because only a small number of sites have two surgeons so there is insufficient data to estimate a two level random effect model effectively. Grade of haemorrhoid and baseline scores for continuous outcomes are included as covariates due to their prognostic value.

For all continuous outcomes the treatment effect estimates (adjusted between arm mean difference) and their 95% CIs and p-values will be based on the model outputs for the treatment arm parameter.

For the non-inferiority outcome (recurrence at 12 months) the treatment effect estimate (adjusted risk difference) and its 95% confidence interval will be based on post-estimation using the delta method and the upper bound of the CI will be used for ascertaining non-inferiority. For the binary secondary outcome (persistence of symptoms at 6 weeks post procedure), the treatment effect estimate (adjusted risk difference) and its 95% CI and p-value will be based on post-estimation using the delta method (see 12.3.4).

Unadjusted analysis (difference between arm and CIs of width outlined above) will be reported alongside adjusted analysis.

12 Primary analysis of Co-Primary endpoints

12.1 Establishing effectiveness of RFA and issues of Multiple Testing

For RFA to be deemed effective it will need to demonstrate both non-inferiority for recurrence at 12 months using both the primary and PP populations (see 12.2.5) and superiority for pain at 7 days (see 12.3.5) so we will not adjust for multiple testing.

12.2 Recurrence at 12 months

12.2.1 Summary measure for recurrence at 12 months

The summary measure is the between arm difference in the proportion experiencing a protocol defined recurrence at 12 months.

12.2.2 Source of recurrence data

Recurrence will be identified using data from patients, GPs, consultants, SAEs and medical notes. For full details see 17.1

12.2.3 Analysis of recurrence at 12 months

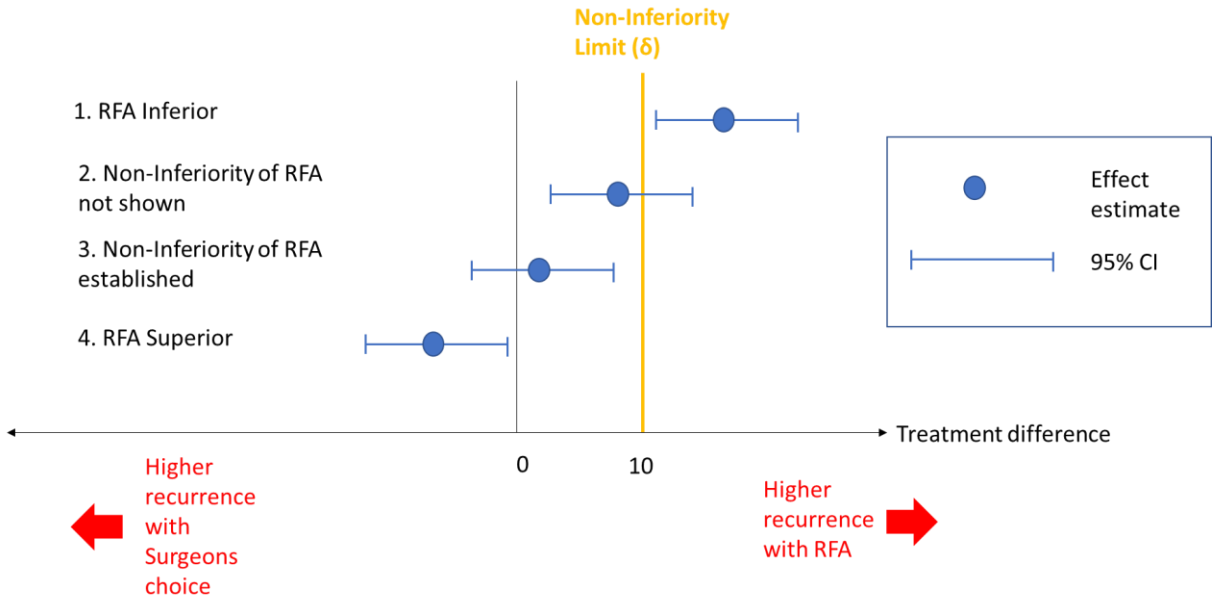
Analyses will use generalised estimating equations (GEE) with a binomial family and logit link with treatment arm and grade of haemorrhoid as fixed effects and surgeon as a random effect. The difference in proportions and its associated confidence interval will be derived using the margins command and its default the delta method. The model can be fitted as shown in the below Stata code.

```
//to set surgeon as the cluster term and fit the model xtset
surgeon_id
xtgee recurrence i.treatment  i.haemorrhoid_grade, family(binomial) link(logit)
//to calculate the difference in risk proportions its CI and p-value using the delta method
margins,  dydx(treatment) level(95)
```

12.2.4 Ascertaining non-inferiority for recurrence at 12 months

For non-inferiority of RFA compared to surgeon choice to be established, the upper bound of the 95% confidence interval will need to be below the non-inferiority margin of 10 percentage points (0.1). For example, CI 3 in Figure 2 would establish non-inferiority, CIs 1 and 2 would not establish non-inferiority and CI 4 would establish superiority.

Figure 2 Illustration of non-inferiority assessment



12.3 Pain at 7 days post treatment

12.3.1 Summary measure for pain at 7 days

The summary measure is the between arm mean difference in the NPRS score at 7 days post treatment. Lower NPRS scores indicate less pain.

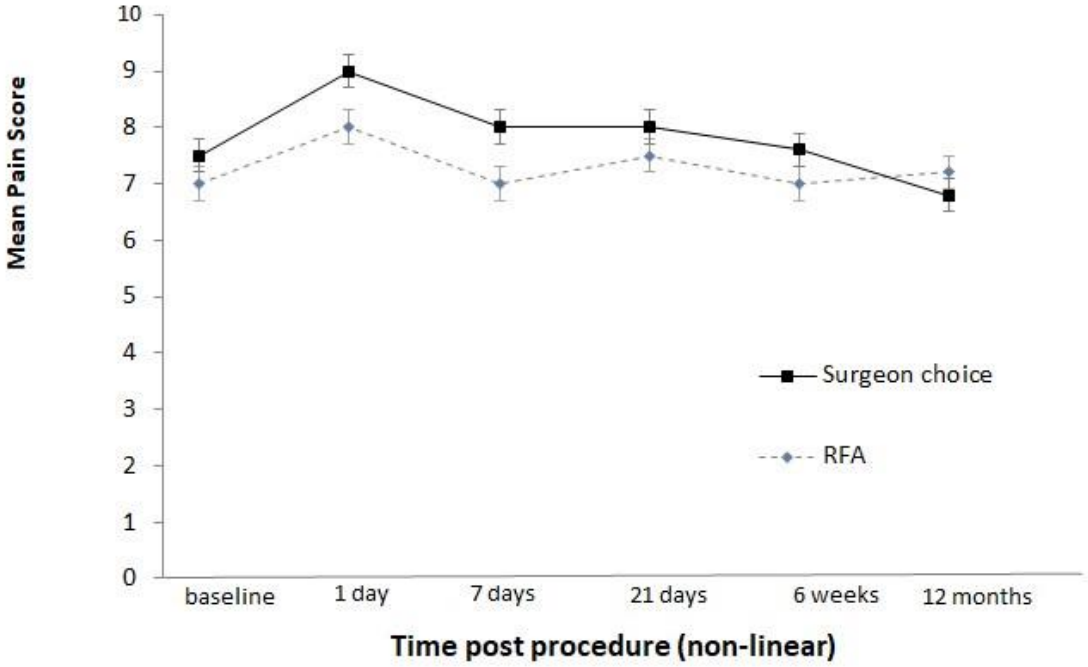
12.3.2 Source of pain data

Pain at 7 days is collected using the NPRS pain rating scale via postal or telephone survey (see 17.3).

12.3.3 Graphical summary of pain outcomes

Although the co-primary outcome is pain at 7 days, we will summarise mean pain scores and associated 95% CIs by follow-up point and arm, as illustrated in Figure 3.

Figure 3 Mean pain scores and 95% CIs by arm for all follow-up assessments



12.3.4 Analysis of pain at 7 days

Analysis will use GEE with an identity link and treatment arm, grade of haemorrhoid and preprocedure pain rating as fixed covariates and surgeon as a random effect. The model can be fitted as shown in the below Stata code.

```
//to set surgeon as the cluster term and fit the model xtset surgeon_id
xtgee pain i.treatment  i.haemorrhoid_grade pain_baseline
```

12.3.5 Ascertaining superiority for pain at 7 days

Lower NPRS scores indicate less pain. If the p-value for the treatment parameter produced by the model is 0.05 or below and the treatment parameter's 95% confidence interval includes the MCID of -0.6 units then superiority of RFA compared to surgeon's choice will have been established.

13 Sensitivity to missing data

13.1 General principles

Case missing data will be imputed using developers rules where available for all outcome measures and analysis populations. Where missing cases exceed developer rule thresholds the response will be considered missing.

To assess sensitivity to missing responses we will use Multiple Imputation using Chained Equations (MICE) for pain at 7 days (see section 13.3) and threshold of change analysis for recurrence at 12 months (see section 13.4). There is no planned sensitivity analysis for missing data for secondary outcomes.

13.2 Missing data summaries

For each co-primary outcome, we will report and describe the proportion of missing data in each group and overall and present descriptive statistics for baseline variables by treatment group and missing data status.

13.3 Expectations about missing data

We expect few exclusions from the mITT population because model covariates (haemorrhoid grade and baseline pain) are collected on the day of surgery. Similarly, recurrence will only be missing if the 12 month follow up forms from patient, consultant and GP are all missing. However, pain at 7 days is collected by telephone and is potentially more problematic. Interpretation of results from the different analysis populations will depend on the extent of missingness (see 8.4).

13.4 Use of MICE for missing pain data

To test sensitivity to missing outcomes and/or covariates data in the mITT population we will undertake multiple imputation using chained equations (MICE) analysis. We will use one hundred multiple imputation data sets and include treatment allocation and baseline covariates in the prediction equation: age, sex, grade of haemorrhoid, weight, BMI and baseline score.. Each variable will be included using the method appropriate for its distributional form or using 'predictive mean matching' in case of non-convergence. We will combine estimates using Rubin's rules. If we observe heavy skew in pain score at day 7, we will consider using the change in pain between baseline and day 7 as the outcome in the multiple imputation rather than pain at day 7.

13.5 Sensitivity to missing data on recurrence at 12 months

If the primary analysis of recurrence at 12 months establishes non-inferiority, we will explore the robustness of this finding to missing data by estimating how many people with missing data in the treatment arm would need to have experienced recurrence to reverse the conclusion (i.e. to bring the upper confidence limit above +10%). Conversely, if the analysis finds that non-inferiority cannot be established, we will estimate the number with missing data in the control arm that would need to experience a recurrence to reverse the conclusion (i.e. to bring the upper confidence limit below +10%).

14 Exploratory analysis of co-primary outcomes

14.1 Subgroup analysis of co-primary outcomes

We will use an interaction statistical test between intervention arm and subgroups to directly examine the strength of evidence for the between arm difference varying between subgroups for the primary outcomes. Age and grade of haemorrhoid will be the only a priori defined subgroups to be considered for interaction test. Subgroup analysis will be performed regardless of the statistical significance on the overall intervention effect.

14.2 Comparison of each surgeon choice procedure with RFA

We will separately calculate the primary outcomes for each of the three surgical options in the control arm. At the discretion of the senior statistician we will calculate the following pairwise differences (and associated 95% CI) if there is sufficient precision to provide an informative comparison:

- RFA and haemorrhoidopexy;
- RFA and, Haemorrhoidal Artery Ligation (HAL)
- RFA and Haemorrhoidectomy.

It should be noted that these are exploratory (and non-randomised) comparisons and not subject to the benefits of randomisation as the characteristics of the control surgery sub-groups may not be balanced when compared to RFA. As such, any comparisons we produce will be caveated appropriately in research outputs. For example, all confidence intervals will inevitably be wider than those of the main comparison, and any CIs overlapping +10% should not be interpreted as evidence that RFA is inferior with this procedure.

15 Analysis of secondary outcomes

15.1 Continuous Outcomes

There are 5 continuous secondary endpoints

- NPRS rated pain score (measured in clinic or by post/telephone survey at 1 and 21 days, 6 weeks and 12 months post procedure)
- Number of days of work lost (measured by research nurse at 6 weeks post procedure). We will also report the number of people who did not miss any days and the number who missed one day or more.
- Haemorrhoid severity score (1 and 21 days, 6 weeks and 12 months post procedure)
- Index (utility) score for EQ-5D-5L [13] (day 1, day 7, day 21, 6 weeks, 1 year post procedure)
- Self-report, 7-item Vaizey incontinence score (6 weeks, 1 year post procedure)

Each time point will be analysed separately and analogously to the primary analysis for pain at 7 days unless plots of residuals against fitted values indicate deviations from normality. If nonnormality is observed, we will consider using a transformation as the dependent variable (all using an analogous model) or, for days of work lost, a Poisson generalised linear model (GLM).

15.2 Binary Outcomes

, Persistence of symptoms at 6 weeks post procedure and dichotomised number of work days missed will be analysed analogously to recurrence at 12 months using a 95% CI but testing for superiority.

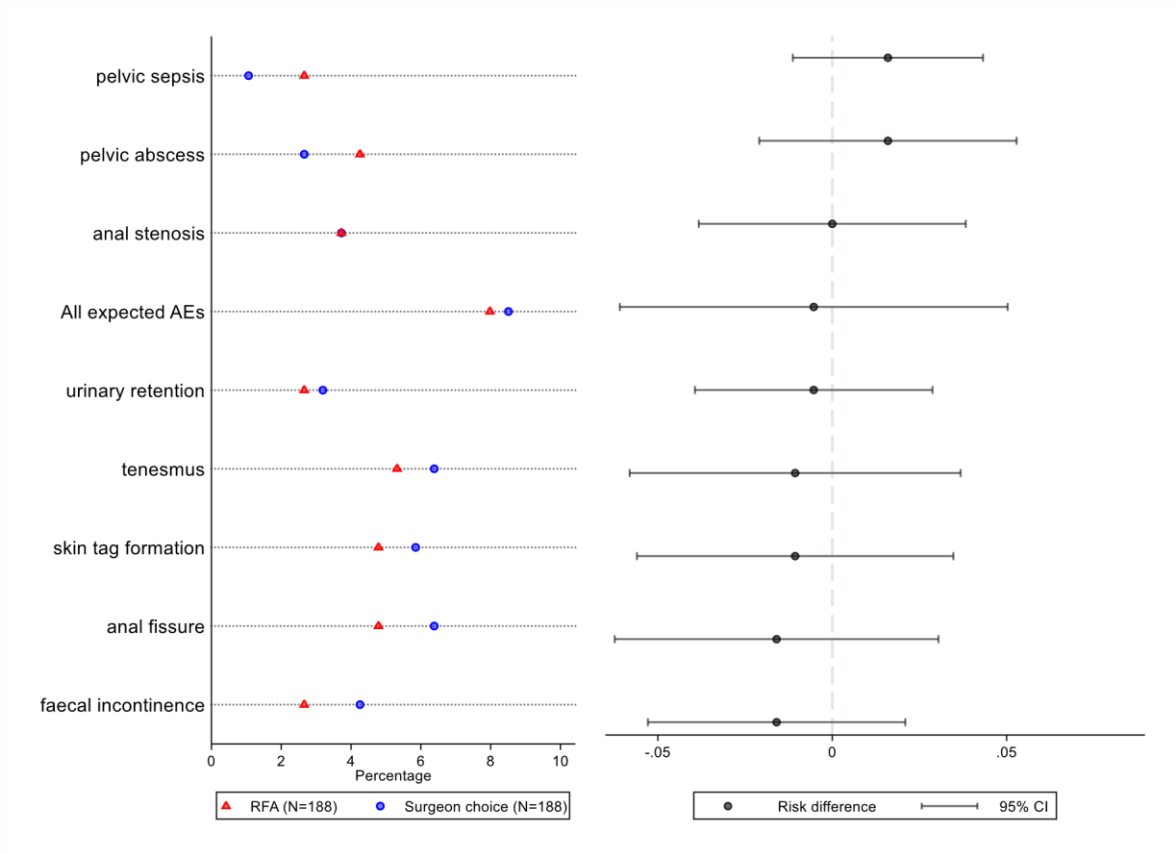
16 Analysis of safety outcomes and complications

Safety outcomes will be analysed using the safety population only (see section 8.1)

Each safety outcome (see section 17.4) will be summarised by arm and time point (during procedure and at 6 weeks and 12 months) using the number of participants experiencing a) each complication type at least once and b) any complication at least once and compared graphically (illustrated using mock data in Figure 4.)

We will also descriptively compare the total number of AEs and SAEs between arms per participant, and overall, by severity, expectedness and expected harm groupings (see list in section 21) and causality.

Figure 4 Comparison of expected AEs by arm



17 Key data definitions and derivations

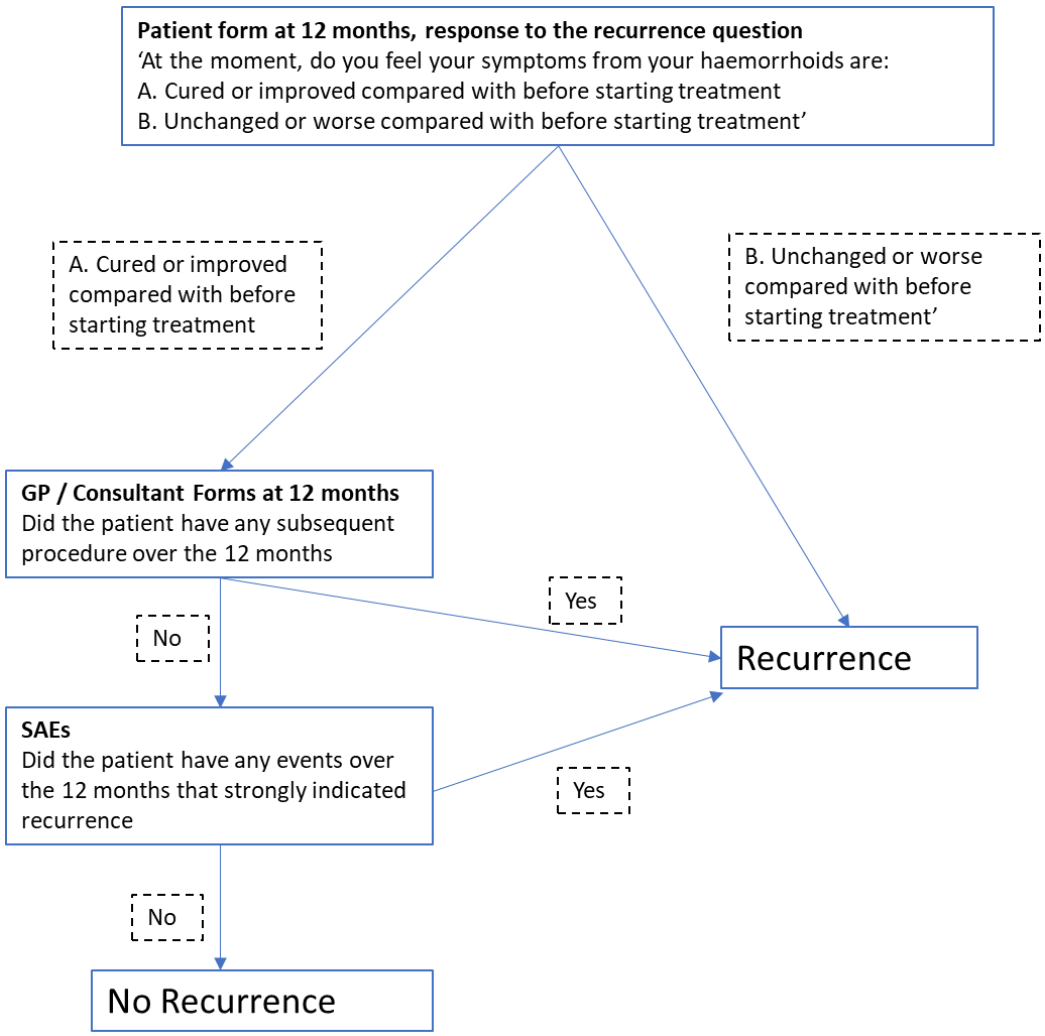
17.1 Recurrence at 12 months

Recurrence at 12 months will be calculated using the patient, consultant and GP follow-up forms at 12 months and SAEs as summarised in Figure 5. To aid with recall, consultants and GPs may also use medical records to complete the 12 months follow up forms.

If recurrence status can be established for at least one of the three forms, that will be taken as sufficient evidence. We will treat the outcome as missing (see section 13) if recurrence status cannot be established from any of the sources. If there is disparity between the forms the decision will be based on the hierarchy in Figure 5.

For patient reported recurrence (see final bullet in 3.2.2) responding A in the top box of Figure 5 would lead directly to "No recurrence"

Figure 5 Calculating recurrence at 12 months



17.2 The numeric pain rating scale (NRPS)

The numeric pain rating scale shows participants a horizontal bar marked with the numbers 0 to 10 from left to right with the words "no pain" above 0 and "worst pain imaginable" above 10 and participants are asked to put a circle around the number that best describes their pain. This question is included on the baseline form and 6 weeks follow up forms (completed in clinic) and the 1, 7 and 21 day and 12 months follow-up forms (completed via telephone or postal survey).

17.3 Clinically relevant collection windows for follow-up assessments

Due to appointment availability, the six-week clinic visit may vary from four to twelve weeks following the intervention. This window is clinically relevant. Other ideal assessment windows are summarised in Table 3

Table 3 Follow up visit ideal windows

Visit	**Ideal follow-up window***
Treatment +1 Day	Treatment +1 Day (or the next Monday if treatment was on a weekend)
+7 days	+6-8 days
+21 days	+18-24 days
+ 12 months	+11- 14 months

17.4 SAEs

AEs and SAEs will be recorded on the AE log at any time during the trial. An SAE is classified as any adverse event, adverse reaction or unexpected adverse reaction that meets the following criteria.

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Is another important medical event

17.5 Complications

Complications are recorded on the 'Procedure details' CRF, the six-week clinical visit and the twelvemonth follow-up.

18 Regulatory guidance and Standard Operating Procedures (SOPs)

The SAP is guided by protocol draft 5 of v6; International Conference on Harmonisation topic E9 [1]; guidance for the content of SAPs in clinical trials [2]; Good Clinical Practice in Clinical Trials [3] and Medicine for Human Use (Clinical Trials) Regulations [4]. All analysis will use internal quality control in line with Sheffield CTRU Standard Operating Procedures (SOPs) using validated statistical software such as Stata, SAS, or R.

19 References

[1] S. R. Brown *et al.*, "Haemorrhoidal artery ligation versus rubber band ligation for the management of symptomatic second-degree and third-degree haemorrhoids (HubBLe): a multicentre, open-label, randomised controlled trial," *Lancet*, vol. 388, no. 10042, pp. 356–364, 2016, doi: 10.1016/S0140-6736(16)30584-0.

[2] S. M. Eldridge, C. L. Chan, M. J. Campbell, C. M. Bond, and S. Hopewell, "CONSORT 2010 statement : extension to randomised pilot and feasibility trials The Consolidated Standards of Reporting Trials (CONSORT) statement reporting of randomised controlled an extension to that statement for," *BMJ Br. Med. J.*, vol. 355, pp. 1–29, 2016, doi: 10.1136/bmj.i5239.

20 Appendix 1 Summary of changes to SAP

Version	Date approved*	Changes	Made by

* And when in relation to any blind/un-blind review or database freeze/lock

21 Appendix 2 List of expected AEs and complications of anaesthesia

Expected AEs associated with the four interventions are:

- tenesmus,
- skin tag formation
- urinary retention,
- bleeding requiring readmission to hospital for transfusion or further intervention,
- anal fissure,
- pelvic sepsis,
- pelvic abscess,
- anal stenosis,
- faecal incontinence
- systemic complications.

AEs defined as complications of anaesthesia are:

- nausea,
- vomiting,
- sore throat,

- dizziness,
- blurred vision,
- headaches,
- bladder problems,
- damage to lips or tongue,
- itching,
- aches and pains,
- pain during injection for drugs,
- bruising and soreness,
- confusion,
- memory loss,
- chest infection, • muscle pains,
- slow breathing,
- damage to teeth,
- worsening of existing medical conditions,
- damage to the eyes,
- heart attack or stroke,
- serious allergy to drugs,
- nerve damage, • equipment failure
- death.