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.

RESEARCH PROTOCOL

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The ORION trial:

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This document describes a clinical trial and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Contents

Abbreviations

Definition of terms

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

1. General information

1.1 Investigator details

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1.2 Clinical Trial Research Unit

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1.3 Sponsor Details

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1.4 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.5 Protocol amendments table

Version number	Amendment Number	Summary of changes
1.2	NSA1	Minor spelling and grammar corrections throughout. Section 4.1 Text corrected to say 12 month follow up for collecting patient unblinding questionnaire (from 6 week). Section 5.2 Addition of pacemakers as an exclusion criteria, due to safety. Addition exclusion of patients who have previously had surgery as part of this trial as recurrence of haemorrhoids is the primary outcome. Table 1 updated to move baseline measures to the day of surgery in reflection of significant waiting time between consent and surgery.
1.3	NSA3	General grammar and spelling corrections throughout. Clarification on NPRS data collection timepoints in outcome measures (section 8.2) for consistency with the data collection table. Description of health economics analysis added (section 11.3).
1.4	NSA4	Amendment to section 5.1 to reflect the flow diagram which specifies that patients with grade II haemorrhoids are eligible if the surgeon deems them suitable for surgery. Amendment to section 5.3 to clarify that patients who have had RBL and/**OR** are considered suitable for surgical intervention may be recruited.

2	SA01	Minor grammatical corrections and updated referencing throughout; addition of trial statistician to CTRU members (p7); clarificiation of trial design (p10); clarification of primary and secondary outcomes/objectives (p 10, 15, 23); change in exclusion criteria to broaden the eligible population to include people that take anticoagulants but which can be safely stopped in time for surgery (p17); addition of nhs.net email account details for consent forms (p18); specification that 6-week follow-up data can be collected as per the clinic format (either face to face or over the phone) (p26); clarification of 'use of assessment instruments' table to include all CRFs (p27-28); clarification and additional description added to sample size calculation and statistical analysis plan (p33-34).
3	SA02	Additional eConsent process added (p19-20)
3.1	NSA9	Updated contents; Amendment to the end of recruitment on page 13 to reflect the agreement of a three-month recruitment extension.
3.2	NSA11	Clarification around the permitted windows for obtaining follow-up data on page 26. Amendment to the end of recruitment and follow-up duration on page 13 to reflect extension of recruitment to January 2024.

1.6 Trial Summary

Study title	The ORION Trial: RadiO fRequency ablation for haemorrhoids
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	NIHR Health Technology Assessment Programme
ISRCTN	14474552
Project start date	01/07/2021
Project end date	31/01/2025

Research Question	For haemorrhoids that are considered appropriate for surgery, does radiofrequency ablation reduce short-term pain, and have long-term recurrence no worse than current recommended interventions?
Aim	To assess whether radiofrequency ablation is at least as good in terms of recurrence rates as existing methods for treating haemorrhoids but superior in terms of post-operative pain. .
Objectives	A full-scale trial that compares the effectiveness of radiofrequency ablation compared to surgeon's choice of surgery for people with haemorrhoids severe enough to warrant surgery.
Trial design	A pragmatic multicentre patient/assessor blind parallel group individual randomised (1:1 allocation) controlled trial with economic evaluation.
Internal pilot/feasibility criteria	Red/amber/green stop/go criteria
Setting	NHS Hospital Trusts
Participants	Patients aged 18 or over who have symptomatic grade II or grade III haemorrhoids considered appropriate for surgery
Intervention	Radiofrequency ablation
Control groups	Surgeon's choice of surgery
Primary outcome(s)	1. Recurrence at 12 months post procedure 2. Pain at 7 days post procedure
Secondary outcome(s)	1. Pain score at 1, 21 days, 6 weeks and 12 months post-procedure 2. Days of work lost 6 weeks post-procedure 3. Persistence of haemorrhoidal symptoms 6-weeks post-procedure

	4. Haemorrhoid severity score 5. EQ-5D-5L at baseline, 1,7,21 days, 6 weeks, 1 year post procedure 6. Vaizey incontinence score at baseline, 6 weeks, 1 year post procedure 7. Health and social care resource use at 6 weeks, 1 year post procedure 8. Complications 9. Cost
Duration of recruitment period and first enrolment date	01/03/2022 – 31/01/2024 (23 months)
Duration of follow-up	Participants will be followed up to 12 months after their procedure
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.

2. Introduction

2.1 Background

Haemorrhoidal tissue forms the ‘anal cushions’ and is a normal component of the anal canal. These are predominantly composed of vascular tissue, supported by smooth muscle and connective tissue. Haemorrhoids result from enlargement of the haemorrhoidal plexus and pathological changes in these anal cushions. They can cause symptoms including discomfort and bleeding and are a common reason for review in a surgical clinic. They are common, affecting as many as 1 in 3 of the population [1]. Over 20,000 operations are carried out each year in England alone [2]. Repeated visits to health care services as well as prolonged recovery after some interventions represents a significant disruption to the personal and working lives of a large proportion of the population.

Treatment is dictated by the degree of symptoms and the degree of prolapse. A tailored approach is advocated by many experts in the field and forms the basis for the most recent guidelines on the topic [3]. After exclusion of other causes to the symptoms, an algorithm of care starts with conservative management in the form of diet and habit modification. Those that remain symptomatic may request intervention. These interventions are influenced mainly by the degree of prolapse. Patients with no prolapse or prolapse on straining and spontaneous reduction may be treated successfully with less invasive outpatient procedures (called “office therapies”), usually in the form of rubber band ligation (RBL). RBL is cheap, easy to carry out and appears very safe. However, it has a high recurrence rate and patients often require further visits to the outpatient department for repeat banding [1].

For those with more extensive prolapse or those who have failed office treatment surgical intervention may be required. These interventions range from haemorrhoidal artery ligation through to stapled haemorrhoidopexy or surgical excision, all requiring either regional or general anaesthetic [3]. Each is associated with a degree of postoperative discomfort, sometimes necessitating overnight hospital stay and a delay in return to normal activity. Recurrence does occur but appears to be lower following more radical procedures, with excisional interventions having the lowest level of recurrence [4]. Taking into account the degree and length of discomfort and potential for recurrence, recent evidence indicates that of these options, open haemorrhoidectomy is the most painful in the short term but results in a better quality of life in the long term

and is the least expensive [5–7]. Nevertheless all three interventions are recommended for use and available on the NHS [3].

An alternative procedure to treat haemorrhoids is the use of radiofrequency ablation (RFA) [8]. RFA is primarily intended for use in patients whose haemorrhoid has failed to respond to less invasive office procedures such as RBL, as well as an alternative to operative procedures for those with a higher degree of prolapse where office procedures are likely to be ineffective [8]. RFA has many potential advantages over the other surgical interventions and is therefore increasing in popularity. It can be done under local anaesthetic, although at present is usually carried out under general anaesthetic in the UK. As the intervention 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. The evidence base for these claims is however limited, mainly from small cohort studies in specialist settings [9–11]. More importantly, the promising longer-term efficacy has not been subject to a randomised comparison.

2.2 Rationale for current study

Haemorrhoidal surgery has been highlighted as one of several conditions where potential savings can be made for the NHS in terms of limitation of surgical intervention and promotion of more conservative therapy [12]. Many patients with symptoms can be treated adequately with non-operative measures.

Nevertheless, there remains a group of patients where conservative therapy has failed or the severity of the disease warrants surgery. For these patients the perfect intervention should be effective whilst at the same time be easy to carry out and convenient for the patient, cause minimal harm and result in rapid recovery whilst remaining cost effective for the NHS [9]. Unfortunately, with many operational procedures, pain is a prominent issue with significant pain lasting up to several weeks in many patients. This quest for the 'perfect', ‘painless’ operation has led to numerous surgical innovations in the last 20 years, many introduced through media hype and industrial promotion to become established therapies before being proven to not quite achieve promoted expectations [9, 13].

Radiofrequency ablation is a promising technique that appears to meet many of the criteria for the ‘perfect' operation, but this has not yet been proven (or refuted) in a

scientifically robust manner. Despite this lack of quality evidence, it is starting to gain traction in terms of take up with increasing private and NHS hospitals offering the service. This uptake is, as with previous interventions, being stirred by media hype and patient expectations [13].

If the RFA procedure can be proved to be at least as effective as current recommended interventions but at the same time be shown to be superior to the patient in terms of reduced inconvenience and more rapid recovery then this uptake can be legitimately incorporated in the treatment algorithm for haemorrhoids, particularly if more cost effective. If on the other hand, the RFA procedure is less efficacious and other outcomes are similar or superior, the NHS will be able to disinvest from introducing the procedure.

The data on radiofrequency ablation is summarised in a recent National Institute for Health and Care Excellence (NICE) overview, which was based on data from about 880 patients from five RCTs and two case series [8]. The overview was summarised by the following statements:

- Current evidence on the safety and efficacy of radiofrequency treatment for haemorrhoids is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
- NICE encourages further research into radiofrequency treatment for haemorrhoids, preferably randomised controlled trials. Outcomes should include pain, secondary haemorrhage, recurrence rate, the need for repeat procedures and quality of life measurements. Details of patient selection should also be reported.

There has only been two further small studies since this overview [10, 11]. Twenty-seven patients were treated with RFA who experienced minimal post-operative pain and recurrence of symptoms in only one patient after a median of 20 months. With the potential increasing uptake of this procedure in the UK combined with the drive to reduce surgical interventions for haemorrhoids the need for urgent research as highlighted by NICE is obvious.

By carefully selecting patients who have failed to respond to conservative measures and comparing this novel intervention with the other procedures currently recommended for this group, we wish to test if the procedure is non-inferior in terms of efficacy. If RFA is shown to be as effective in terms of recurrence, functional outcome and quality of life but also more cost effective than alternatives, then this will have significant implications for the adoption of RFA in the NHS. However, if this is not the case, this would allow the NHS to disinvest in RFA.

3. Aims and objectives

3.1 Research Question

'For haemorrhoids that are considered appropriate for surgery, does radiofrequency ablation reduce short-term pain, and have long-term recurrence no worse than current recommended interventions?'

3.2 Aim

To assess whether radiofrequency ablation is at least as good in terms of recurrence rates as existing methods for treating haemorrhoids but superior in terms of post-operative pain.

3.3 Objectives

An internal pilot to determine the feasibility of recruiting to a full-scale trial (see section 8.4).

A full-scale trial that compares the effectiveness of radiofrequency ablation compared to surgeon's choice of surgery for people with haemorrhoids severe enough to warrant surgery. The primary objectives will compare:

i) Recurrence at one year
ii) Pain at day 7

The secondary objectives will compare:

iii) Pain at day 1, day 21, 6-weeks and 1 year post-procedure
iv) Number of days of work lost (measured by research nurse at 6-weeks post-procedure)
v) Persistence of haemorrhoidal symptoms 6-weeks post-procedure
vi) Haemorrhoid severity score

vii) Health and social care resource use (6 weeks, 1 year post-procedure)Quality of life (measured on the EQ-5D-5L before randomisation, 6 weeks, 1 year post-procedure)

viii) Vaizey incontinence score (6 weeks, 1 year post procedure)

ix) Complications

x) Costs

4. Trial Design

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

4.1 Blinding

Patients are blinded to the operation they receive (RFA or the surgeon's choice of intervention. Usual practice is for all interventional 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) [14]. In this situation it is more likely that participants will become unblinded.

For participants undergoing GA, complications are similar across the interventions and it is unlikely that participants will be able to view their anus directly. 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 database 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. Patients will not be told which operation they will receive, due to the possibility of long-term follow-up.

4.2 Unblinding

The Data Monitoring & Ethics committee (DMEC) for the study will be able to request unblinded data and recommend study termination to the Trial Steering committee (TSC) on the grounds of safety or futility.

The operation details will be recorded in the patients' medical records. In the event of a medical emergency the care team will be able to access treatment allocation through the medical records. If unblinding is required, please refer to the ORION unblinding manual for further instructions.

5. Selection of participants

5.1 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 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 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.

We aim to recruit 376 participants (188 per arm). Patients with grade II haemorrhoids who have failed one episode of banding and/or the surgeon feels operative intervention is appropriate, or those with grade III haemorrhoids are eligible for the trial. Potential participants will therefore fall into two groups:

1. Patients presenting to the surgical outpatient clinic (SOPC) with symptomatic haemorrhoids that are considered suitable for office therapy such as RBL. These will mainly be grade II haemorrhoids (haemorrhoids with no prolapse or those that prolapse on straining but spontaneously reduce) and patients will have failed conservative therapy. Such patients will undergo office treatment if appropriate whilst at the same time being informed of the study. Those that fail RBL or decline RBL and request surgical intervention will be then offered entry into the trial.

2. Patients presenting to the SOPC with symptomatic haemorrhoids that are considered unsuitable for office therapy such as RBL and who require surgical intervention. These will mainly be grade III haemorrhoids (haemorrhoids with prolapse that needs manual reduction) and patients will have failed conservative therapy. These patients will be informed of the trial and offered entry before their operation date.

5.4 Informed consent process

The trial will be coordinated from the Clinical Trials Research Unit (CTRU) in Sheffield School of Health and Related Research (ScHARR). A member of the patient's care team at individual sites will identify and consent potential participants. Potential participants will receive an approved Participant Information Sheet (PIS) and given the opportunity to ask questions from both the surgical and research team at their NHS Trust. No study related procedures will occur before the approved consent form is signed, other than initial case note review for eligibility. There is an additional, optional consent question asking for permission for Sheffield CTRU to securely store the contact details

of participants and allow these researchers to contact the participants for the follow-up questionnaires, should the patient's care team be unable to fulfil this role.

For each participant, the original copies of the signed consent forms will be retained by the investigator in the site file but must be made available for inspection by the study monitor. Patients will also receive a copy of the PIS and their signed consent form to keep, and a copy will be filed in their medical notes and a copy posted to Sheffield CTRU. Consent will be reconfirmed at each study visit, as recommended by Good Clinical Practice Guidelines. A screening log will be maintained for each site, to document all potential participants screened, whether they were recruited, and any reasons for non-recruitment where this information is available.

5.4.1. Face-to-face consent

Patients will be referred to an outpatient clinic. They will be provided with a PIS and given sufficient time to read and discuss this (ideally 24 hours) prior to consent. Patients with investigations excluding pathologies other than haemorrhoids will be phoned by the research nurse before the follow-up clinic visit to ascertain whether they meet the eligibility criteria and if they are interested in entering the trial. They will then be seen in clinic by the consultant and research nurse or on the day of surgery. If the patient is assessed as eligible for the study and they agree to participate, informed written consent will be taken. A copy of the consent form should be filed in the investigator site file and a scanned copy mailed to the Sheffield CTRU. ORION team; sth.oriontrial@nhs.net .

5.4.2. Remote consent

Postal consent: As an alternative to face-to-face consent, recruiting sites may also use postal consent. Patients will be posted out a PIS alongside two copies of the postal consent form. Delegated research personnel may also call patients to provide an overview of the trial and answer any questions. Once the patient has read the PIS, and if they agree to take part, they will complete the two copies of the consent form. One copy will be kept by the patient for their records and the other will be posted back to the research team in the stamped addressed envelope provided. As with face-to-face consent, the patient should have sufficient time between receiving the PIS and signing the consent forms (ideally at least 24 hours). Once the research nurse receives the signed consent form, they will call the patient to complete the postal consent review

form. The original consent form should be filed in the investigator site file, a copy filed in the patient's medical notes and a copy mailed to the Sheffield CTRU, alongside a copy of the postal consent review form. If the patient is interested in the study but did not return the consent forms then they will be consented face to face at their next clinic appointment or on their day of surgery.

Verbal confirmation of written consent: As an alternative to face-to-face consent, recruiting sites may also use verbal confirmation of written consent. Patients will be posted an invitation letter with a PIS and the postal consent form. Delegated research personnel will contact the potential participant by phone and conduct the consent discussion. As with face-to-face consent, the patient should have sufficient time between receiving the PIS and being telephoned to request verbal consent and signing the consent forms (ideally at least 24 hours). They will ask the participant to initial, sign and date the consent form during the discussion. The designated research staff member will document the discussion in the patient medical notes and complete the Verbal Confirmation of Consent Review Form. The participant will be asked to bring the consent form with them when they attend their surgery or to post the form back. If the participant has not returned their consent form on the day of surgery, a delegated member of the ORION team will reconsent the patient. The consent form will be filed in the ISF and two copies will be made; one will be given to the patient and one put in the patient's medical notes. A signed consent form must be received by the site study team before baseline data are collected and surgery is conducted.

5.5 Co-enrolment guidelines

Concurrent participation in any other clinical trial is not allowed for the duration of the study. Co-enrolment with observational studies should be discussed with the TSC. At the point of entry into the trial, patients should not already be taking part in an interventional trial.

6. Trial treatment

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.

6.1 Participants randomised to Radiofrequency ablation (RFA)

6.1.1Procedure Details

Radiofrequency ablation is increasingly available to the NHS through the Rafaelo® device. It is an adaptation of technology widely used to treat varicose veins. Modified for the treatment of haemorrhoids, a special needle probe is inserted into the haemorrhoidal cushion, through which radiofrequency energy is applied, aiming to restrict its blood supply causing it to necrose and fall away, relieving the patient of their symptoms.

In the UK, RFA is generally performed under general anaesthesia with the patient positioned in lithotomy. It can be performed under local anaesthetic. A proctoscope (Fcaresystems, Antwerpen, Belgium) with a simple vent on one side, through which a single haemorrhoidal tissue protrudes, is placed in the anal canal. At a level approximately 5 mm above the dentate line, 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. The Rafaelo® device and associated HPR45i probe (F care systems, Antwerpen, Belgium) are used to deploy RFA energy of 4 MHz frequency to the haemorrhoidal tissue. The tip of the probe is inserted fully into the haemorrhoid tissue approximately to a depth of 5–10 mm, at an approximately 30° angle to the tissue surface. The haemorrhoidal tissue is tilted away from the submucosal layer. The application of RFA is continued until the tissue exhibits whitish discolouration, after which the energy is applied to the external surface of the haemorrhoidal tissue to optimize tissue desiccation. An optimum of 3000 Joules with a power sitting of 25 W is applied to an individual haemorrhoidal tissue at one time. A cold saline-soaked tonsillar swab is immediately applied to the surface of the haemorrhoidal tissue. Any bleeding is controlled by inducing coagulation using the radiofrequency probe [11].

The company that supplies the equipment also provides training courses on how to carry out the procedure. All surgeons involved in the study will have completed this training and, in addition, will have carried out at least five procedures prior to recruiting to the study.

RFA has NICE approval where there are arrangements for clinical governance, consent and audit or research [8]. The device is used within its licensed indication without modification and therefore does not require MHRA approval.

6.1.2 Participant procedure

Participants will undergo standard supportive care for a surgical intervention as per local procedures. This will usually be in the form of available clinical contact for any concerns as well as access to clinicians responsible for the participant care if appropriate.

6.2 Patients randomised to surgeons choice of other procedures currently available on the NHS

The alternative therapy that is offered for this group of patients in the UK is varied and depends to a certain extent on the preference of the surgeon. Stapled haemorrhoidopexy, haemorrhoidal artery ligation and haemorrhoidectomy are all available on the NHS and appropriate conventional therapies according to international guidelines [3] and the control arm will therefore comprise the 'surgeon's choice' of operation based on one of these three options. All surgeons involved in the study will have carried out at least five of any of the procedures they perform in the trial, prior to recruiting to the study.

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. It is done with the use of a stapling gun. Three haemorrhoid stapling devices are commonly in use within the UK (Johnson & Johnson, Chex, and Covidien). Reflecting the pragmatic nature of the trial, surgeons are able to use the gun which they normally use in their routine practice.

Haemorrhoidal Artery Ligation (HAL) uses a proctoscope modified to incorporate a Doppler transducer. This enables accurate detection of the haemorrhoidal arteries feeding the haemorrhoidal cushions. Accurate ligation of the vessels with a suture reduces haemorrhoidal engorgement. When combined with a 'pexy' suture, both bleeding and haemorrhoidal prolapse is addressed. All surgeons participating in the trial will ensure the need for a pexy suture is routinely assessed and recorded. The procedure is simple, uses existing surgical skills and has a short learning curve, with the manufacturers recommending at least 5 mentored cases before independently practicing.

Haemorrhoidectomy involves one of two commonly used traditional excisional procedures done across the world: open and closed. Both have the intention of excising the haemorrhoidal cushions whilst preserving healthy intervening mucocutaneous bridges. The procedure is most commonly done with electrocautery. In this trial, surgeons will undertake whichever procedure they would do as part of their routine practice. The use of the Ligasure Medtronic (Minneapolis, MN, USA) and Harmonic Ethicon Johnson and Johnson (NJ, USA) devices to perform an excisional haemorrhoidectomy will also be included.

7. Randomisation and enrolment

Once eligibility has been confirmed and baseline data recorded (see section 9), participants will be centrally randomised using the CTRU online randomisation system (SCRAM). Participants will be randomly allocated to either the RFA arm 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. Randomisation will be stratified by centre. The statistician will be blinded to the treatment allocation until the database is frozen.

8. Outcomes

8.1 Primary outcomes

1. Recurrence at 12 months post procedure, defined as per the HubBLe trial [7]
2. Numeric Pain Rating Scale (NPRS) daily at 7 days post-procedure [15]

8.2 Secondary outcomes/endpoints

1. NPRS (1, 21 days, 6 weeks, 1 year post procedure)
2. Number of days of work lost (measured by research nurse at 6 weeks post procedure)
3. Persistence of symptoms at 6 weeks post procedure
4. Haemorrhoid severity score [16]
5. EQ-5D-5L[17] (baseline, day 1,day 7, day 21, 6 weeks, 1 year post procedure)
6. Self-report, 7-item Vaizey continence score (6 weeks, 1 year post procedure)[18]

7. Health and social care resource use questionnaire (6 weeks, 1 year post procedure)
8. Complications (see table 1)
9. Cost.

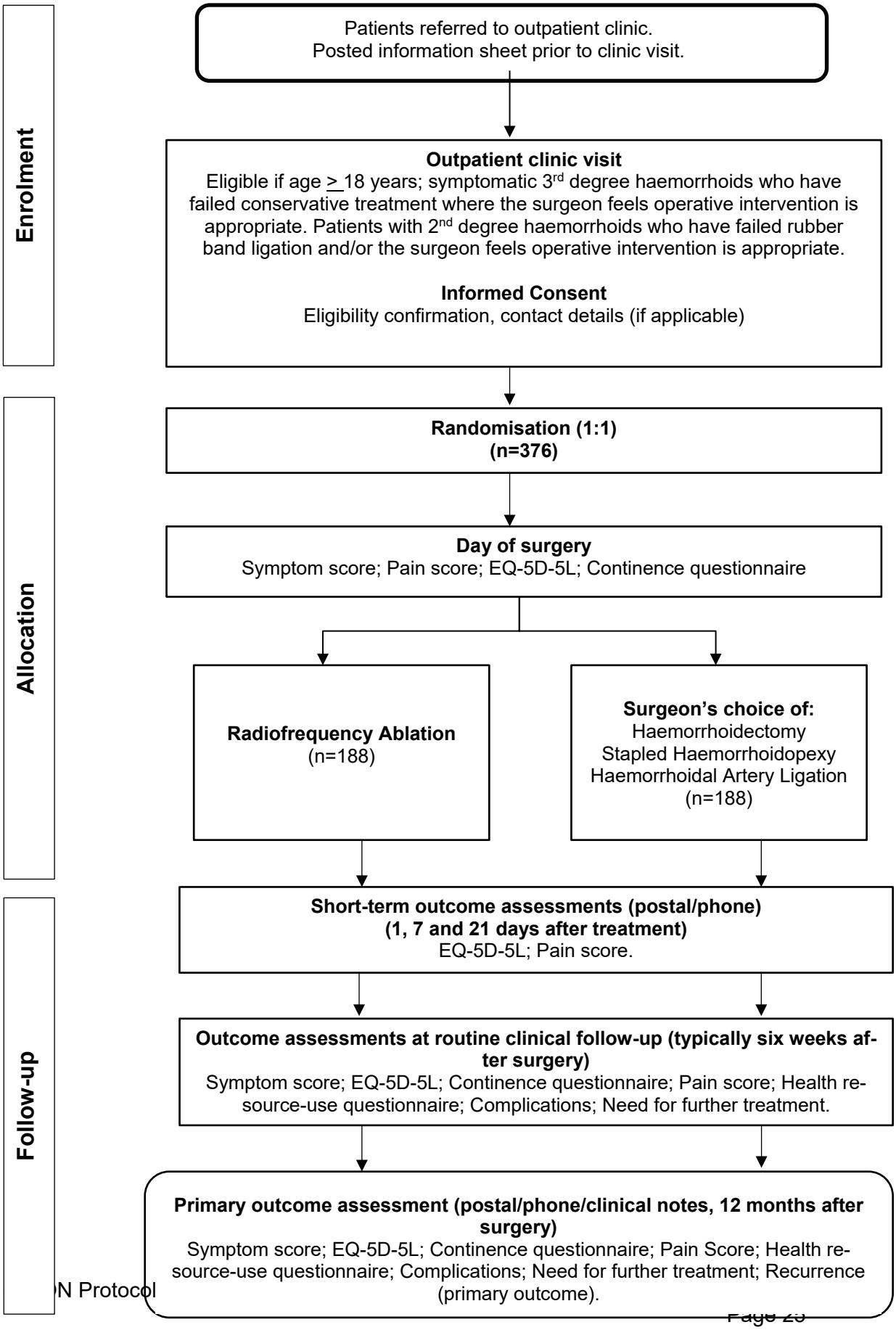
8.3 Feasibility Outcomes

The initial phase of the trial will be an internal pilot, which will follow best practice recommendations [19]. The internal pilot trial will run in at least eight sites, with the aim of starting all 15 sites by the end of the pilot. The progression criteria will be applied to data collected from the beginning of Month 9 (projected March 22) to the end of Month 14 (projected August 22). Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocols based on the recruitment, assessed against the following red/amber/green stop/go criteria, with assumed site initiation dates based on the recruitment estimates.

● **Green - go:** based on the HubBLe trial [7], an average of two participants per site per month over six months (124 participants; 100% of 6-month target; 41% of final 12- month target).
● Amber - funder discretion: 83-123 participants (67% to 99% of 6-month target; 27% to 40% of final target).
● Red - stop: fewer than patients per hub per month (less than 67% of 6-month target; less than 27% of final target).

The progression criteria will be assessed by the Trial Steering Committee at the end of the following month. The progression criteria will be based on recruiting at least 50% (83/124) of the target for these first six months. Clinical and patient-reported outcome data from the internal pilot will be included in the final analysis.

8.4 Study Flowchart



9. Assessments and procedures

Outcome data will be collected by research nurses, consultants and specialist nurses either in person at SOPC (baseline data, 6 weeks follow-up if the usual clinic is face-to-face) or by telephone questionnaires (data for day 1,7,21 and 12 months post-operatively, and at 6-weeks if the usual clinic format is by telephone) or by completed postal questionnaire (12 months post-operatively). In addition, the 12-month data on recurrence, complications, resource use and need for further treatment will be supplemented by hospital/GP note review (Table 1). In the instance of disparity of responses between the consultant/hospital notes, SAEs reports, consultant and GP records and the participant, the CI will act as the ultimate arbitrator. In the scenario of no response from the patient with regards to recurrence but with another procedure to treat haemorrhoids in their medical notes, this will be recorded as a recurrence. Measuring recurrence based on SAEs will be treated via a case-by-case basis. For example, bleeding within 2-3 days of procedure which subsided would not be categorized as a recurrence, but uncontrolled episodes later on would.

The following windows are permitted for collection of follow up data. However, where these windows are missed due to patient availability rather than an error at site, a protocol non-compliance will not be recorded.

- Day 1: As soon as possible if not collected on day 1
- Day 7: -/+1 days (i.e. between days 6 and 8)
- Day 21: -/+3 days (i.e. between days 18 and 24)
- 6 weeks: -2/+6 weeks (i.e. between weeks 4 and 12)
- 12-months: -1/+2 months (i.e. between months 11 and 14)

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. All aspects of data management will be provided by the Sheffield CTRU in accordance with their own standard operating procedures.

CTRU's in-house data management system (Prospect) used for the capture and storage of participant data, uses industry standard techniques to provide security, including password authentication and encryption. Access to Prospect 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 protocol. 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 12 months. Due to appointment availability the six-week clinic visit may actually vary from four to twelve weeks following the intervention; this window is seen as clinically relevant.

9.1 Study assessments schedule

Table 1 – Use of assessment instruments during the trial

	Eligibility and consent	Randomisation	Baseline (day of surgery (-4wks))	1 day post procedure	7 days post procedure	21 days post procedure	6 weeks post procedure	1 year post procedure
Eligibility & consent (incl. demographics)	●							
Medical history	●							
Randomisation		●						
Physical examination			●					
EQ-5D-5L			●	☎	☎	☎	●	☎/🗋
Numeric Pain Rating Scale			●	☎	☎	☎	●	☎/🗋
Vaizey incontinence score			●				●	☎/🗋
Haemorrhoids severity score			●				●	☎/🗋
Procedure Details			●					
Post-surgery details			●					
Complications review interview							●	☎/🗋

Days of work lost							●	
Health and social care resource use							●	☎/🗋*
Need for further treatment questionnaire							●	☎/🗋*
Recurrence (Primary outcome)							●	☎/🗋*
Clinical appearance at proctoscopy (where applicable)							●	
Participant unblinding interview								☎/🗋
Consultant questionnaire								☎/🗋
GP Questionnaire								☎/🗋

Key: ● – assessment in clinic; ☎/🗋- telephone/postal self-report assessment;

*supplemented by hospital/GP notes.

9.2 Procedure for assessing safety

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 clinical visit and at the twelve-month follow-up.

If there are any clinical concerns (including mental distress) about a participant, identified through any of the research procedures or assessments, these will be referred to the appropriate clinical team for further investigation. This includes responses to questionnaires that cause concern about the participant's wellbeing, and any other concerns aside from the expected symptoms for haemorrhoids. 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).

9.3 Participant withdrawals

Participants may wish to withdraw from the trial, or there may be a clinical need to withdraw the participant. Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/discontinuation form and the patient notes, and no further data will be collected for this participant for the study. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. 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.

Excessive participant withdrawal from follow-up has a negative impact on a study. Research staff will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Nevertheless, if participants do not wish to remain in the study their decision must be respected.

9.4 Lost to follow-up

Participants will be defined as lost to follow up if they do not attend or contribute data at the month 12 visit. If a participant is lost to follow-up, this will be recorded in the CRF using the study completion/discontinuation form.

10. Safety Reporting

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 twelve-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. These SOPs have been developed to comply with guidance from the National Research Ethics Service, which is a subdivision of the National Patient Safety Agency, and Good Clinical Practice (GCP). 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 REC within 15 days of becoming aware.

We will record the occurrence of the following complications that are associated with the four interventions: tenesmus, skin tag formation and urinary retention, bleeding requiring readmission to hospital for transfusion or further intervention, anal fissure, pelvic sepsis, pelvic abscess, anal stenosis, faecal incontinence and systemic complications. Additionally, occurrences of the following complications of anaesthesia will be recorded: 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 and death.

10.1 Definitions

Term	**Definition**
Adverse Event (AE)	Any untoward medical occurrence in a study participant.
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that : • Results in death • Is life-threatening*

	• Requires hospitalisation or prolongation of existing in-patients' hospitalisation** • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Is otherwise considered medically significant by the investigator***
Related AE/SAE	An AE or SAE which is related to a research procedure
Notable Event	An event of particular interest that does not necessarily meet the criteria for seriousness but requires expedited reporting as per the protocol.

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

AEs and SAEs are defined as an event that occurs after the patient has provided written informed consent for trial entry and within 12-months of the last administration of trial treatment.

All related AEs will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious (see section 10.1). Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

SAEs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event. The CTRU will notify the Sponsor of each of these events.

10.3 Study specific exemptions

There are no expected SAEs.

10.4 SAE notification procedure

Site staff will be responsible for reporting all SAEs. Once an SAE has been identified, a member of the site research team will complete an SAE form, notifying the site's PI and send this to the CTRU.

All SAE forms must be sent by fax to 0114 222 0870 or email to ctru-saes-group@sheffield.ac.uk. Receipt of the initial report should be confirmed within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day.

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.

10.5 CTRU responsibilities

The Sponsor will delegate CTRU responsibility for the reporting of SAEs to the regulatory authorities and the research ethics committee, as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

10.6 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

11. Statistics

11.1 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 Intraclass 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 which found a 12% drop-out in the HAL surgery arm and a zero ICC for 12-month recurrence [7]. 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.

11.2 Statistical Analysis

Analyses of recurrence will be performed using generalised estimating equations (GEE) with a binomial link in which the fixed effect covariates are treatment arm and grade of haemorrhoid, with surgeon being incorporated as a clustering term. The difference in proportions and its associated confidence interval will be derived using the delta method [20]. Pain scores at day 7 will be analysed using GEE with an identity link; the fixed effect covariates will be treatment arm, grade of haemorrhoid and pre-procedure pain rating, with surgeon again incorporated as a clustering term. Secondary endpoints will be analysed analogously. Unadjusted analysis (difference between arm and 95% CIs) will be reported alongside adjusted analysis.

Safety will be assessed by i) post-surgical complications and ii) postsurgical complications leading to SAE, both of which will be summarised for each arm by the number of participants experiencing a) each complication type at least once and b) any complication at least once. A full statistical analysis plan will be developed before unblinded data are made available.

The primary analysis will use the modified Intention to Treat (mITT) population (we do not follow-up participants who drop out before surgery). For the primary outcomes only, Per Protocol (PP) and As Treated (AT) populations will be considered for sensitivity analysis. There is no a priori defined sensitivity analysis for secondary 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 sub-groups to be considered for interaction test. Sub-group analysis will be performed regardless of the statistical significance on the overall intervention effect.

Case and item missing data will be examined and multiple imputation methods will be used to reduce bias due to any missing responses in the analyses. Where appropriate, modelling methods that generate robust standard errors (SEs) in the presence of missing data will be considered.

We will separately calculate the primary outcomes for each of the three surgical options in the control arm and will calculate for each of them the difference (and associated 95% CI) between 1) RFA and haemorrhoidopexy; 2) RFA and, Haemorrhoidal Artery Ligation (HAL) and 3 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.

11.3 Cost effectiveness analysis

The primary economic analysis will be a within trial analysis, comparing Radio Frequency Ablation to surgeons' choice (of three options commonly used in the NHS), over a one-year time horizon.

Subgroup analyses of RFA compared to the three comparator options separately will be presented but will of course be more uncertain since the trial is designed for the blended comparator, not the three surgical options separately.

Analysis of EQ5D-5L will be undertaken as part of the main statistical analysis (see section 11.2) and will be performed using the recommendations from NICE in place at the time of analysis for the appropriate value set in the base case. Other approaches will be included as sensitivity analyses. Analyses will also be performed for the five different responses.

For the cost-effectiveness analysis, the area under the curve method will be used to analyse EQ5D and estimate Quality Adjusted Life Years (QALYs) for each individual. Resource use is collected for the following categories: the direct costs of surgery, the costs of treating recurrence, other complications, and any other relevant NHS resource use.

An NHS perspective will be used for costing resource use.

Unit costs, to apply to each category of resource use will come from sources widely used in economic evaluations such as NHS Reference Costs, NHS supply systems, British National Formulary and 'Unit Costs of Health and Social Care' published by the PSSRU. Where necessary, we will supplement these unit costs with local sources such as the finance departments of participating hospital trusts.

The analysis will use multiple imputation methods for missing data. For each individual we will estimate total costs and QALYs over the one year follow-up period. The mean costs and QALYs for each comparator will be estimated and regression analysis used to adjust for baseline characteristics of patients assigned to each arm. Bootstrap methods will be used to generate the cost-effectiveness plane and associated cost-effectiveness acceptability curve.

12. Trial supervision

12.1 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.

12.2 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.

12.3 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 supervised 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.

13. Data handling and record keeping

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. All participants will be assigned a unique study ID number at screening that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres. All CRFs will only identify the participant by their study ID number

Study records, including source data, will be stored for 10 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 10 years after the last patient last visit. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 10 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 10 years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc or USB flash drive) with the paper files. Archived documents will be transferred to the Sponsor before destruction.

13.1 Archiving

Data held by the CTRU will be stored in accordance with the CTRU archiving Standard Operating Procedure (*SOP PM012 Archiving*). Archived documents will be logged on

a register, which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

14. Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The research staff at each site will enter data from source documents into the study specific Prospect database when available. After data has been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will be anonymised and will only be identifiable by the participant's study ID number. No patient identifiable data will be transferred from the database to the statistician. Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.

14.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow-up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research

- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capability to conduct the trial will be assessed and documented. The CTRU will arrange a site initiation visit with each site or carry this out remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

14.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures.

Central and/or on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Site Monitoring Plan (SMP).
The level of risk will be agreed with the Sponsor. Central and on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Trial Monitoring Plan (TMP). This will include (at a minimum):

1. Source Data Verification (SDV)
2. SAEs/SUSARs – reported to the Sponsor and followed up to resolution
3. Resolution of data queries
4. Investigator site file maintenance
5. Training records for site staff (trial specific and GCP) and appropriate delegation of duties
6. Patient consent procedures
7. Reporting of protocol non-compliances

14.3 Reporting serious breaches and non-compliances

A “serious breach” is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC within 7 days of becoming aware of a serious breach. All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

14.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP.

A site initiation visit will be performed or carried out remotely at/for each participating site before each site recruits their first participant. During this visit/remote contact, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Regular site monitoring visits will occur throughout the study as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data is authentic, accurate and complete.
2. Safety and rights of the patient are being protected
3. The study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the CRF against Investigator’s records by the Study Monitor (source document verification) (see section 13 for further details on data collection). The study Monitor will

contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs.

A close-out visit will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

14.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to post consent forms to CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial.

15. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

Information throughout the course of the study may be disseminated at conferences and other events, providing this does not relate to any endpoint, but these must be with the approval of the Chief Investigator, and the funder must be informed with sufficient notice.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

16. Finance

The ORION trial is funded by The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (reference NIHR131861). Participants will not be reimbursed for their time in the trial. Further funding details are included in the site agreement.

17. Ethics approval & regulatory compliance

Before initiation of the study at participating site, the protocol, informed consent forms and information materials to be given to the participants will be submitted to the REC/HRA. Any further amendments will be submitted and approved by the HRA and ethics committee.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place. The study does not require further regulatory approvals as all interventions are offered routinely as standard care.

18. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval. A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites. Recruitment of study participants will not commence at a site until a letter of Confirmation of Capacity and Capability (CCC) has been issued.

19. Trial Organisation and Responsibilities

19.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their site and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI

will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

19.2 Sheffield Clinical Trials Research Unit (CTRU)

The CTRU at The University of Sheffield will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU Trial Manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability (CCC) has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

20. Patient & Public Involvement (PPI)

PPI members guided 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.

Two patients from initial PPI exercises are to be co-applicants. These members 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 TMG meetings in between. Patient representatives not on the project team

will also be invited to join the TSC. Expert patients sit on the study management committee, representing patient concerns and inputting into the study conduct and analysis. 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 TMG. Training and mentorship will be provided by Sheffield CTRU. All PPI involvement will be reimbursed according to the INVOLVE guidelines.

21. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study.

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