



The HubBLE Trial: Haemorrhoidal Artery Ligation (HAL) versus Rubber Band Ligation (RBL) for haemorrhoids

A multi-centre randomised controlled trial comparing rubber band ligation with haemorrhoidal artery ligation in the management of symptomatic second and third degree haemorrhoids.

Version 8.0; 4th June 2013

Sheffield Teaching Hospitals 
NHS Foundation Trust



Clinical
Trials
Research
Unit.

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

Sponsor reference: 16063

University of Sheffield reference: 128786

HTA reference: 10/57/46

REC reference: 12/YH/0236

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Glossary

AE	Adverse event
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
CTRU	Clinical trials research unit
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GP	General Practitioner
HRQoL	Health related quality of life
HTA	Health Technology Assessment
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
OH	Open haemorrhoidectomy
PI	Principle Investigator
QALY	Quality adjusted life year
R&D	Research and Development
RBL	Rubber band ligation
RCT	Randomised control trial
REC	Research ethics committee
SAE	Serious adverse event
ScHARR	School of health and related research
SH	Stapled haemorrhoidopexy
SOP	Standard operating procedure
SOPC	Surgical outpatient clinic
STH	Sheffield Teaching Hospitals
TMG	Trial management Group
TSC	Trial Steering Committee
VAS	Visual analogue scale

1. Project Details

1.1. Investigator details

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1.3 Title of project

A multi-centre randomised controlled trial comparing rubber band ligation with haemorrhoidal artery ligation in the management of symptomatic second and third degree haemorrhoids.

Short title:

The HubBLE trial: Haemorrhoidal Artery Ligation (HAL) versus Rubber Band Ligation (RBL) for haemorrhoids.

1.4 Sheffield Teaching Hospitals project reference number

16063

1.5 Protocol version number and date

Version 8.0, 4th June 2013

1.6 Sheffield Teaching Hospitals Directorate affiliation

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2. Research Question

Main research question: does haemorrhoidal artery ligation have a lower recurrence rate than rubber band ligation when used to treat second and third degree haemorrhoids?

Secondary research questions: which of the two procedures is more cost-effective; which is least painful; which has fewest complications and which has the greatest effect on the patients' quality of life?

3. Abstract

Haemorrhoids are a very common condition seen in surgical clinics. After exclusion of more sinister causes of haemorrhoidal symptoms (rectal bleeding, perianal irritation and prolapse), the best option for treatment, depends upon persistence and severity of the symptoms. Minor symptoms often respond to conservative treatment such as dietary fibre and reassurance. For more severe symptoms (particularly prolapse), treatment such as rubber band ligation may be therapeutic and is a very commonly performed procedure in the surgical outpatient setting. Surgery is usually reserved for those who have more severe symptoms, as well as those who do not respond to non-operative therapy. Surgical techniques include treatments which excise the haemorrhoidal cushions (haemorrhoidectomy) or those which preserve the cushions but reduce the vascular engorgement and replace the cushions to a more anatomical position (stapled haemorrhoidopexy). Although rubber band ligation (RBL) has the advantage of being non-operative, easy to perform and minimally invasive, there is a risk of complications, chiefly pain. Importantly the recurrence rate after RBL is high, particularly for more severe levels of prolapse even after repeat RBL. More recently, haemorrhoidal artery ligation has been introduced as a minimally invasive, non destructive surgical option. Although it requires anaesthetic for its performance, recovery is rapid, the complication rate is low and the recurrence rate may be significantly lower than that of rubber band ligation. Such an operation may be a very good option for those with haemorrhoids who wish to consider a more definitive therapy or those who have not responded to initial rubber band ligation.

We aim to test whether rubber band ligation or haemorrhoidal artery ligation is a more clinically effective and cost effective method of treatment for those with symptomatic second or third degree haemorrhoids by comparing the two techniques with a randomised controlled trial in a multi-centre setting.

4. Aims of the Study

The aim of this study is to establish the clinical effectiveness and cost effectiveness of haemorrhoidal artery ligation compared with conventional rubber band ligation in the treatment of people with symptomatic second or third degree (Grade II or Grade III) haemorrhoids.

The primary objective is to compare patient-reported symptom recurrence at 12 months following the procedure.

The secondary objectives are to compare post-operative:

- symptom severity score (adapted from Nystrom et al.[1]);
- health related quality of life (using the EuroQol-5D “The EuroQoL group”[2]);
- continence (using the validated Vaizey Incontinence Score[3]);
- pain (using a 10 cm visual analogue scale);
- surgical complications;
- need for further treatment;
- clinical appearance of haemorrhoids at proctoscopy following recurrence;
- health care costs;
- cost effectiveness.

5. Background

Haemorrhoidal tissue, which forms the ‘anal cushions’, is a normal component of the anal canal and is composed predominantly of vascular tissue, supported by smooth muscle and connective tissue. Haemorrhoids result from enlargement of the haemorrhoidal plexus and pathological changes in the anal cushions. They are common, affecting as many as 1 in 3 of the population[4]. Approximately 23,000 haemorrhoidal operations were carried out in England in 2004/5[5] and the prevalence may be even higher in professionally active people. Repeated visits to hospital for therapy represent a significant disruption to the personal and working lives for this population in particular.

Treatment is dictated by the degree of symptoms and the degree of prolapse, and ranges from dietary advice to rubber band ligation (RBL) in the outpatient department, to an operation under general or regional anaesthetic. Although RBL is cheap, it has a high recurrence rate and patients often require further visits to the outpatient department for repeat banding before exploring surgical options[6]. Although there are some variations (such as ligasure haemorrhoidectomy), surgery is commonly traditional “open” haemorrhoidectomy (OH) or a stapled haemorrhoidopexy (SH); both require an anaesthetic. OH is associated with considerable post-operative discomfort, sometimes necessitating overnight hospital stay and a delay in return to normal activity, but has a low recurrence rate; SH has a slightly higher recurrence rate but is carried out as a day case and patients return to normal activity more quickly[7]. An alternative treatment is haemorrhoidal artery ligation (HAL), which also requires an anaesthetic, but is thought to enable even quicker return to normal activity. Recurrence rates are reportedly similar to SH but complication rates are lower[8].

There are substantial data in the literature concerning efficacy and safety of RBL including multiple comparisons with other interventions[9-15]. Recurrence varies from 11% to over 50%. This broad range probably reflects the definition of recurrence (patient symptoms or clinical appearance), the grade of haemorrhoids treated (grade I no prolapse; grade II spontaneously reducible prolapse; grade III prolapse requiring manual reduction; and grade IV un-reducible prolapse), the number of treatments and/or the intensity and length of follow up. In most studies, the incidence of recurrence is more than 30% and appears greatest for grade III haemorrhoids. Pain is common for a few hours following RBL and occasionally patients experience pain so severe as to require admission to hospital (around 1%[6]), bleeding (3-4%, sometimes necessitating further treatment[13]) and vaso-vagal symptoms (3%[16]). There have also been rare incidences of blood transfusion [17, 18] and severe pelvic sepsis with a few instances leading death[16]. Recurrences can be treated by re-banding or by surgical intervention.

Although HAL requires an anaesthetic, evidence suggests a recovery similar to RBL but an effectiveness that approaches the more intensive surgical options. The substantial data concerning effectiveness includes one recent systematic review[8], three Randomised Control Trials (RCTs)[19-21], one non-randomised trial[22] and over 20 case series. A recent overview has been carried out by the National Institute for Health and Clinical Excellence (NICE), which concludes that current evidence shows it to be a safe alternative to OH or SH[23], this is summarised below.

- In terms of efficacy, studies with more than 1 year follow up suggest bleeding, pain on defecation and prolapse (surrogates of recurrent symptoms) in 10%, 9% and 11% of patients respectively
- Regarding safety, post-operative haemorrhage requiring intervention (readmission, transfusion, reoperation or correction of coagulopathy) was reported in less than 1.2%, haemorrhoidal thrombosis was seen in less than 3.5% and fissure formation in less than 2.1%
- The data from the three RCTs comparing HAL with SH and OH is difficult to combine, but efficacy seems similar for all procedures, with OH perhaps being superior in treating prolapse, although it is unclear if a "pexy" stitch was used in the HAL cases to reduce prolapse. OH appears to lead to the most post-operative pain and longest recovery. There are conflicting results as to whether the HAL technique results in less pain compared with SH. Complications were also more frequent in the OH group but occurred at a similar frequency when SH and HAL were employed.

Both the systematic review and the NICE overview highlight the lack of good quality data as evidence for the advantages of the technique; most data is from case series. Even the RCTs have significant methodological drawbacks that make them subject to selection, performance, attrition and detection bias. Indeed none of the studies are powered to reach any meaningful conclusion. There are no existing studies that compare HAL with RBL.

6. Plan of Investigation

6.1 Methodology

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

Potential participants will fall into three groups:

1. Patients presenting to the surgical outpatient clinic (SOPC) with symptomatic haemorrhoids that do not require further tests. This group will be identified by the clinical team from the GP referral letter and a patient information sheet sent to them prior to their clinic appointment. If they are willing to participate they will be consented and randomised when they attend the appointment.
2. Patients presenting to the SOPC with symptomatic haemorrhoids that require further tests to exclude other diagnoses. This group will be identified by the clinician at the clinic appointment and given a patient information sheet. They will undergo the necessary outpatient tests (usually endoscopy) and if negative (i.e. the symptoms are due to haemorrhoids) they will be contacted by the research nurse prior to attending their follow-up clinic appointment. They will then be randomised and consented when they re-attend the clinic.
3. Patients who return to SOPC following one unsuccessful RBL. They will be identified by the clinician at their first clinic appointment (when they have RBL) and given a patient information sheet. They will be contacted prior to a follow-up appointment (usually six weeks after treatment) by a research nurse. If they remain symptomatic and are willing to participate, they will be consented and randomised when they re-attend.

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

After consent, participants will be individually randomised to HAL or RBL in equal proportion at all centres using a remote, web-based randomisation system.

The CTRU will co-ordinate follow-up and data collection in collaboration with the UK centres. Participant study data will be collected and recorded on 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.

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.

6.2 Study Design

A multi-centre, parallel group randomised controlled trial.

6.3 Statistical and health economic analyses

A full statistical analysis plan will be developed prior to database lock. It is not anticipated that any interim analyses will be performed for efficacy.

Differences in the primary outcome, recurrence of haemorrhoids between the two treatment groups, will be analysed using logistic regression adjusting for sex, age at surgery and history of previous intervention as fixed effect covariates and surgeon as a random effect. This permits the calculation of odds ratios and their confidence intervals for the effect of HAL relative to traditional RBL adjusting for the effects of covariates and the clustering by surgeon. Further detailed analysis of haemorrhoid recurrence will be performed by analysing the length of time to recurrence under a Cox-proportional hazards model adjusting for the same covariates. The secondary outcome of pain, as measured on the visual analogue scale (VAS), with repeated measures will be analysed under a multi-level longitudinal approach adjusting for the same covariates. The secondary outcome of procedural complications (pain from thromboses, bleeding requiring consultation, fissuring of the anal canal), elicited during the complications review interview or from the patient notes at 6 weeks and one year post surgery, will be compared between the two groups at each time point using Poisson regression which accounts for the essentially random nature with which complications arise, although care will be taken to note whether there is any clustering by surgeon. The emphasis of all analyses will be on estimating effect sizes of HAL surgery on recurrence rates and other outcomes in comparison to standard treatment with RBL, and as such appropriate confidence intervals will be reported for all estimates.

We will collect data as part of the trial that will allow us to conduct a full economic evaluation. The main economic analysis will focus on estimating the incremental cost per quality adjusted life year (QALY) of HAL versus RBL over the 12 month follow up period of the trial in: a) patients with new haemorrhoids; and, b) patients with recurrence following RBL. We will also present results in terms of the incremental cost per recurrence avoided.

The time horizon compares to 12 months used in an evaluation of SH versus RBL in patients with grade II haemorrhoids conducted alongside a pilot clinical trial[24] and 3 years in a modelling study comparing SH and OH[5]. The former study recommended larger trials and longer follow up. Since it

is likely that both surgical complications and recurrence rates will differ at 12 months we will also use decision modelling to extrapolate beyond the trial outcomes. We will draw on and develop as appropriate the model reported in the HTA report[5]. This model is also being considered for adaptation alongside a model that includes RBL, by those conducting the eTHoS trial (HTA 08/24/02) of stapled haemorrhoidopexy (SH) vs. traditional haemorrhoidectomy (OH). We will liaise with the eTHoS project team to ensure consistency, where appropriate, in our approaches to model adaptation. This will include issues around both model structure and time horizon, as well as parameter values where these are common to both decision problems. This will also avoid unnecessary duplication of workload, particularly in relation to reviewing.

Both modelled and within-trial estimates of cost effectiveness will adopt a NHS perspective. Within the trial, recording of resource use for each patient will focus on the initial surgical intervention received and follow up events. Case report forms will be developed and used to record the duration of the procedures and operators involved, anaesthetic time (for HAL), duration of hospital stay by location and any medication use. Subsequent contacts with primary or secondary care and repeat procedures will also be recorded. We will use case note review to identify secondary care resource use, whilst primary care resource use will be identified via patient questionnaires (health and social care resource use questionnaire – see table in 6.10) at the 6 week visit and 12 month contact, and also with the GP at 12 months.

Unit costs for each of these items will be drawn from published, national sources where feasible (for example, Personal Social Service Research Unit “Unit costs of health and social care”) and supplemented with data from trust finance departments where required. Standard approaches to annuitisation of capital equipment will be applied using the same discount rate as in the rest of the analysis (3.5% as per current NICE guidance).

Patients will be asked to complete the EQ-5D instrument at pre-randomisation, pre-surgery (baseline) and 1 day, 7 days, 21 days, 6 weeks and 12 months following the treatment. The UK population tariffs will then be used to calculate QALYs for each patient. EQ-5D has been applied in previous studies in this area[24] and appears to be sensitive to changes in patient outcomes. Pain is likely to be one of the main symptoms in which we might expect the treatments to differ and this is well reflected in the EQ-5D instrument.

In addition, we will explore the relationship between EQ-5D values and specific complications and symptoms, such as relapse, incontinence and pain. We will also consider the relationship between EQ-5D and the combined symptom severity score. These explorations may prove valuable to future modelling studies in this area as there is evidence that previous studies have been hampered by limited utility data. Indeed, a specific recommendation of a recent HTA study was “that further research should include RCTs which collect a generic HRQoL measure such as the EQ-5D or SF-36 at follow-up times close to the procedure and, in the long term, calculate an estimate of preference-based utility. Baseline data from a trial of this kind would also provide a better estimate of HRQoL and utility of patients with symptoms.” (p.88 HTA report[5])

We will use appropriate statistical techniques to reflect skewness, repeated measures from individual patients and the clustering of the patients, by surgeon and within different centres. Parameter uncertainty will be fully reflected in the estimates by generating a cost effectiveness

acceptability curve. We will also consider other forms of sensitivity analysis to reflect further sources of uncertainty.

6.4 Outcome Measures

6.4.1 Primary outcome measure

'Recurrence', defined as the proportion of patients with recurrent haemorrhoids at 12 months, as derived from a telephone assessment in combination with GP and hospital records. Patients who have undergone further treatment during the follow up period will be considered to have recurrent haemorrhoids.

The trial is a pragmatic design with a dichotomous outcome. As no validated symptom score exists, we have based our definition of recurrence on Shanmugam et al.'s systematic review[9] definition:

*"1. Cured or improved: Symptom free or mild residual symptoms but not requiring further treatment at the end of study period; or,
2. Unchanged or worse: No symptom improvement and requiring further intervention or suffered complication or deterioration of symptoms."*

This study will simplify Shanmugam's criteria into the following question, asked at 12 months by a research nurse:

'At the moment, do you feel your symptoms from your haemorrhoids are:

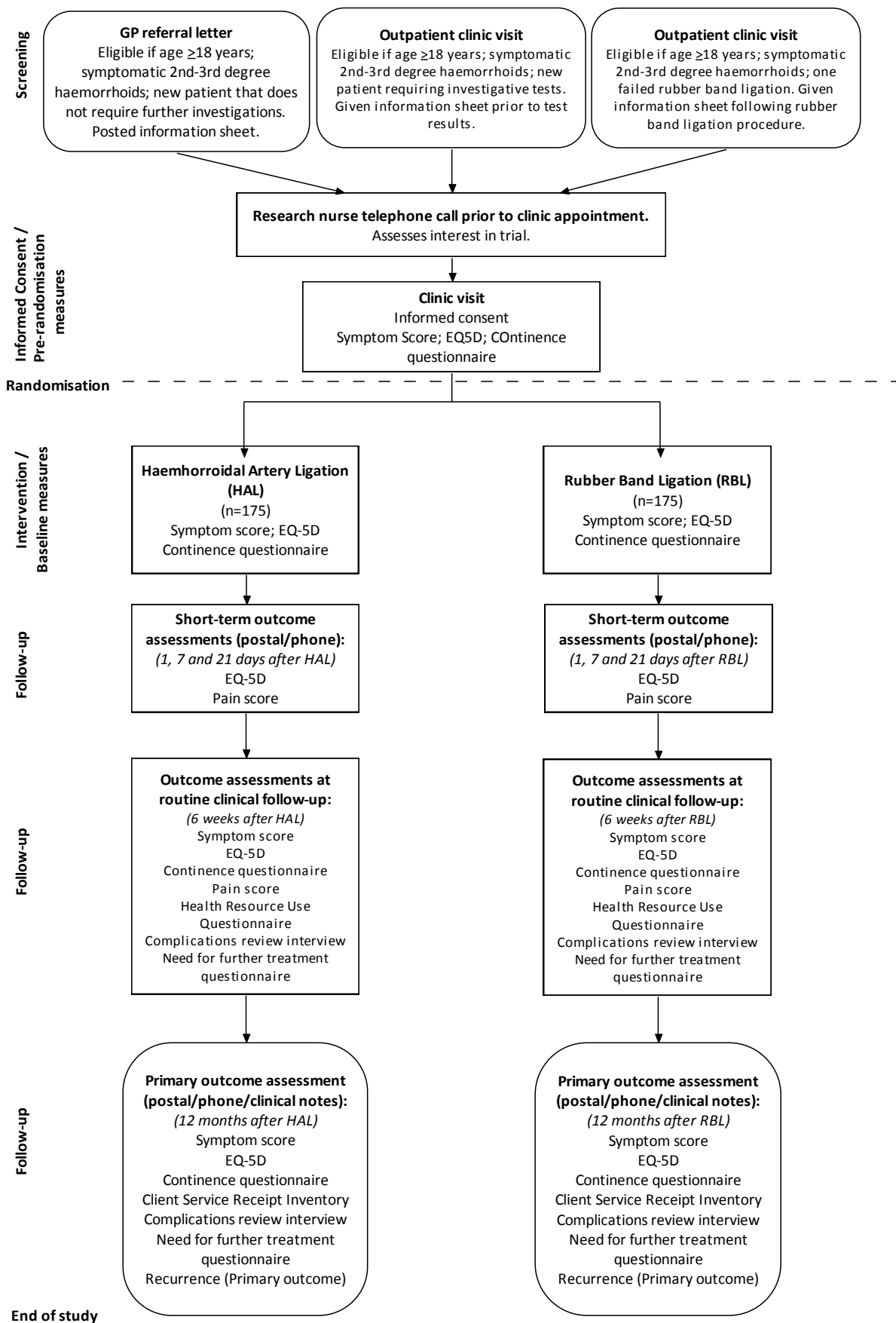
1. Cured or improved compared with before starting treatment; or,
2. Unchanged or worse compared with before starting treatment?'

Any patient who answers '1' but has required further treatment since the initial procedure will be reclassified as '2', identified via hospital records, their consultant, their GP and patient questioning.

6.4.2 Secondary outcome measures

1. Symptom score (pre-randomisation, pre-surgery, 6 weeks, 1 year);
2. EQ-5D (pre-randomisation, pre-surgery, 1, 7, 21 days, 6 weeks, 1 year);
3. Continence questionnaire (pre-randomisation, pre-surgery, 6 weeks, 1 year);
4. Pain score (VAS, pre-randomisation, pre-surgery, 1, 7, 21 days, 6 weeks);
5. Health and social care resource use questionnaire (6 weeks, 1 year);
6. Complications review (6 weeks, 1 year);
7. Need for further treatment including details (6 weeks, 1 year);
8. Clinical examination findings if recurrence (6 weeks)

6.4.3 Study Flow Chart



6.4.4 Measurement of outcomes

Eligible patients who have given written informed consent to participate in the study will undergo a pre-randomisation assessment (Symptom score, EQ-5D, Continence questionnaire, height and weight) and pre-surgery (baseline) assessment on the day that they receive their allocated treatment (Symptom score, EQ-5D, Continence questionnaire); if the patient's procedure is on or within 7 days of the date of randomisation, patients do not need to complete the pre-surgery (baseline) questionnaire on the date of procedure. After their procedure, patients will be asked to complete questionnaires one, seven and twenty-one days after surgery (EQ-5D, Pain score). At six weeks, further data will be collected at the routine follow-up clinic visits (Symptom score, EQ-5D, Pain score, Continence questionnaire, Health and social care resource use questionnaire, Complications review interview, Need for further treatment questionnaire). Finally, one year after their procedure, they will be sent questionnaires (Symptom score, EQ-5D, Continence questionnaire, Health and social care resource use questionnaire, Complications review interview, Need for further treatment questionnaire, Recurrence) and be followed up by telephone. We will measure recurrence (the primary outcome) at 12 months.

6.5 Project Setting

Sheffield Teaching Hospitals NHS Foundation Trust (STH) will be the 'clinical co-ordinating centre' and house the Chief Investigator. A further 11 to 13 centres will be approached to recruit patients and deliver the trial. Coordination of the trial will be by the CTRU. Recruitment will take place in outpatients, RBL may take place in outpatients or theatre, depending on the trust's current practice and HAL will take place in theatre.

6.6 Participants

6.6.1 Eligibility

The target population will be patients referred to collaborating centres for treatment of haemorrhoids.

Inclusion criteria:

- Adults aged 18 years or over with symptomatic second or third degree haemorrhoids.

Exclusion criteria:

- Patients that have had previous surgery for haemorrhoids (at any time)
- Patients that have had more than one injection treatment for haemorrhoids in the past 3 years
- Patients that have had more than one RBL procedure in the past 3 years
- Patients with known perianal sepsis, inflammatory bowel disease, colorectal malignancy, pre-existing sphincter injury
- Patients with an immunodeficiency
- Patients that are unable to have general or spinal anaesthetic

- Patients currently taking Warfarin Clopidogrel or have any other hypocoagulability condition
- Patients currently taking Nicorandil
- Pregnant women
- Patients that are unable to give full informed consent (this may be due to mental capacity or language barriers)
- Patients previously randomised to this trial

6.6.2 Proposed sample size

Assuming the proportion of patients who experience recurrence following RBL is 30% and following HAL is 15%, the sample size required to detect a difference in recurrence rates with 80% power and 5% significance is 121 individuals per group. In order to account for any between-surgeon variation and loss to follow-up, we propose increasing this to 175 per group. This increase is based on the conservative assumption that there will be 14 surgeons in the trial (one per centre) and intra-class correlation (ICC) of 2.5% in keeping with typical ICCs observed by Ukoumunne[25]. A more likely scenario is that each site will have a minimum of two surgeons, in which case the power to detect this difference is 85%; if there is no between-surgeon variation, the power will be 90%. Because the surgical procedure is well-developed and standardised, intra-class correlation should be virtually zero and the proposed sample size should have closer to 90% power.

The impact of loss to follow up will be minimal for the primary endpoint (haemorrhoidal recurrence at 12 months). Patients who do not complete their 12-month follow-up will have their hospital notes reviewed and their GP will be written to in order to ascertain whether any complications or operative procedures were recorded. The only drop-out expected would be where the patient dies, moves out of the area, or has no traceable patient notes, and we anticipate this would be less than the 5% we have now allowed for in this patient population (a previous study of RBL which used only clinical follow up, reported a 1-year loss to follow up of 10%[26]).

6.7 Recruitment

6.7.1 Patient pathway

It is our perception that, when given the choice of RBL or HAL at the first clinic visit, a significant proportion of patients will elect for RBL. However, there is an opportunity to recapture a proportion of these patients if the RBL subsequently fails as they will be re-approached for recruitment at this time.

6.7.2 Expected throughput of eligible patients

Two audits have been carried out to assess the throughput of eligible patients at the lead centre:

- At STH on average 2 patients per colorectal clinic are eligible for the study. Four surgeons (each running 2 clinics per week) have undergone the necessary training and have the experience to recruit for the study. Assuming a pessimistic estimate of 5 clinics per week

across a forty week year (taking into account annual leave, emergency commitments etc.) this extrapolates to 200 eligible patients per year from the lead centre;

- A subsequent audit of one surgeon's practice from the lead centre during a 6 month period suggests 7 patients per month undergo HAL and 16 patients per month undergo RBL. All would be eligible for the study. Extrapolation of these figures suggest this surgeon alone sees 276 eligible patients over 12 months;

6.7.3 Eligible : consent ratio

There is good evidence that trials which compare non-invasive medical procedures with invasive surgical procedures involving a general anaesthetic have problems consenting eligible patients. Eighty two per cent of problems preventing "type 3" surgical trials (those where the comparator is medical or minimally invasive) are related to patients' equipoise[27]. On average, such trials take between three and four times as long to recruit[28]. Consent rates are often far below those of trials comparing similar surgical interventions, with expected consent rates often being below 20%.

6.7.4 Time spent per patient screened

Our assumptions are that every patient screened will cost a research nurse three hours in terms of liaison with the clinical team to ensure potentially eligible candidates are flagged; posting information about the study in advance of screening visits; time taken to get to screening visits in clinics; screening, information giving and discussion of equipoise issues; consent and randomisation where required. For every patient recruited we anticipate 38.5 hours recruitment (service support) work (£808), assuming a screened:randomised conversion rate of 1 in every 13. Recruiting 39 patients would require 1500 hours (roughly 0.7 WTE over one year, or, £31,426.33 at each centre for Year 1).

6.7.5 Coverage and Rationalisation

There are an estimated 2 eligible patients available per clinic; with an estimated four surgeons involved at every centre and an estimated four clinics per centre per week, there is clearly a challenge for recruiting research nurses to be available for all potentially eligible patients (coverage). Given the anticipated equipoise issue and screened:randomised ratio (see above), it is imperative that as many potentially eligible patients are screened as possible. A key function of the research nurse may be to work with clinical teams to channel potentially eligible patients into particular clinics (especially where multiple surgeons share a waiting room) so that the research nurse can use their time more efficiently and the number of eligible but unscreened patients is minimised (rationalisation).

6.7.6 Feasibility Phase

After the initial set up period of 8 months we will run the first wave of recruitment as an internal pilot trial to assess the feasibility of trial recruitment plans. The Trial Steering Committee (TSC) will assess the feasibility of the trial after four months of recruitment. We will need to recruit 350 people in total to account for an anticipated 5% loss to follow-up at 12 months (primary outcome

assessment time point), giving us 90% power to detect a difference between HAL (n=175) and RBL (n=175).

We anticipate recruiting up to 117 participants in the first four months with an anticipated eight centres recruiting. However, given that trial recruitment is usually asymptotically distributed and that we anticipate having 15 centres open to recruitment by the fifth month of recruitment, we would still anticipate reaching our 12 month recruitment target if we fell short of this target. So, we propose a minimum of 35 (10%) participants in the first four months after randomisation for continuation. Processes will be included to try and identify the reasons for numbers unwilling to randomise and excluded due to factors such as language challenges.

6.7.7 Non-recruited Data Collection

In order to follow CONSORT guidelines[29]for reporting RCTs we will collect aggregate anonymised data on non-recruited patients. These patients will fall into three groups: eligible patients refusing consent, eligible patients not recruited by the clinician and ineligible patients.

To satisfy the requirements of the CONSORT will collect basic baseline data for eligible patients (those that have refused consent and those not recruited by the clinician) along with a reason for their non-recruitment and the patient's preference and intended management (i.e. which procedure they opt for in treating their haemorrhoids). To complete the CONSORT diagram, we will collect baseline data and reasons for ineligibility for patients referred for treatment of grade II and III haemorrhoids at the participating centres.

6.8 Intervention

The intervention is either RBL or HAL. Both interventions are established and well documented procedures. Both intervention arms are considered standard care by NICE.

Conventional RBL uses a simple suction device that is applied to each haemorrhoid via a disposable proctoscope. A rubber band is then fired onto the base of the haemorrhoid which constricts the blood supply causing it to become ischaemic before being sloughed approximately 1-2 weeks later. The resultant fibrosis reduces any element of haemorrhoidal prolapse that may have been present. This is a very commonly performed procedure in all SOPCs; figures from an audit of current practice at STH over 20 such procedures are carried out every week. The procedure is a basic surgical skill that all senior staff are familiar with and competent in performing.

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 practising. All

surgeons involved in the study will have completed this training and in addition will have carried out over 5 procedures prior to recruiting to the study.

6.9 Safety Assessments

We will collect data on the Adverse Events (AEs) which are considered related to the study treatment including but not limited to those listed below as expected events on the CRFs. Any complications that occur following the intervention will be identified on the 'Procedure details' CRF and any further complications will be identified at the six week clinic visit and at the 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.

6.9.1 Possible Expected Outcomes for Rubber Band Ligation

Very common (affecting more than 1 in 10 patients) outcomes following this procedure include pain, which is common for a few hours after the procedure and recurrence. Common outcomes following this procedure include bleeding and fainting (affecting approximately 1 in 25 people). Uncommon complications include admission to hospital for bleeding requiring blood transfusion (affecting less than 1 in 500 people) and admission to hospital for pain, usually necessitating removal of bands (affecting approximately 1 in 100 people). Rare and very rare (affecting less than 1 in 1,000 or 1 in 10,000 people) complications include severe infection.

6.9.2 Possible Expected Outcomes for Haemorrhoidal Artery Ligation

Common (affecting less than 1 in 10 patients) outcomes following this operation include pain, bleeding, anal fissure and pain on defaecation. Uncommon (affecting less than 1 in 100 patients) outcomes following this operation are postoperative haemorrhage, bleeding requiring re-admission to hospital and recurrence of haemorrhoids. Rare (occur in less than 1 in 1000 people) complications could include urinary retention, pelvic sepsis, pelvic abscess, anal stenosis, faecal incontinence and systemic complications.

6.9.2.1 Side effects and complications of anaesthetic

Common (affecting less than 1 in 10 patients) side effects from anaesthetic include feeling sick and vomiting, sore throat, dizziness, blurred vision, headaches, bladder problems, minor damage to lips or tongue, itching, aches and pains, pain during injection for drugs, bruising and soreness, confusion and memory loss. Uncommon (affecting less than 1 in 100 patients) side effects from anaesthetic include chest infection, muscle pains, slow breathing, damage to teeth, an existing medical condition

getting worse. Rare or very rare (affecting less than 1 in 1000 or 1 in 10,000 people) complications are damage to the eyes, heart attack or stroke, serious allergy to drugs, nerve damage, equipment failure. Deaths caused by anaesthesia are very rare. There are probably about five deaths for every million anaesthetics in the UK.

Details of any of the AEs listed above will be recorded on the case report forms and participant completed questionnaires and reported periodically to the Sponsor, Data Monitoring Committee (DMEC) and the Trial Steering Committee (TSC).

6.10 Outcome Assessment Instruments

1. EQ-5D quality of life score [The EuroQoL group]
2. Visual analogue pain score
3. Vaizey incontinence score[3]
4. Haemorrhoids symptom score[1]
5. Complications review interview
6. Health and social care resource use questionnaire
7. Need for further treatment questionnaire
8. Recurrence questionnaire
9. Clinical examination findings (if recurrence at 6 weeks)

Table 1 – Use of assessment instruments during study.

	Pre-Randomisation	Randomisation	Pre-surgery (Baseline) / Intervention	1 day	7 days	21 days	6 weeks	1 year
EQ-5D	○		○	●	●	●	○	●
Visual analogue pain score	○		○	●	●	●	○	
Vaizey incontinence score	○		○					●
Haemorrhoids symptom score	○		○				○	●
Randomised		○						
Surgery – RBL or HAL			○					
Complications review interview							○	●*
Health and social care resource use data							○	●*
Need for further treatment questionnaire							○	●*
Recurrence (Primary outcome)								●*
Clinical appearance at proctoscopy (where applicable)							○	

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

6.11 Quality Control & Assurance

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

- the Trial Steering Committee (TSC);
- an independent Data Monitoring and Ethics Committee (DMEC);
- Trial Management Group (TMG).

These committees will function in accordance with Sheffield CTRU SOPs. As a minimum, the TSC will consist of a neutral chair with clinical and research expertise in colorectal surgery and a patient representative. The Committee will meet every 6 months from the start of the trial. The DMEC will consist of an independent statistician and two independent surgeons with clinical trial expertise. The TMG will comprise of a 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. The trial involves a CE-marked device used for its intended purpose and therefore falls outside the remit of Statutory Instruments 2002 no. 618 and 2008 no. 2936.

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

7. Project Management

Sheffield Teaching Hospitals NHS Foundation Trust will act as the sponsor for the trial, and therefore will have overall responsibility for the trial along with the Chief Investigator (employed by STH). The study will be registered with the local R&D department of each participating centre and a Principal Investigator will be responsible for the study at their site

Data management will be provided by the CTRU who adhere to their own SOPs relating to all aspects of data management including data protection and archiving. The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of participant data. Prospect 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.

8. Expertise

The research team has the expertise to cover all aspects of the research and the right blend of multidisciplinary skills – clinicians, experienced trialists, statisticians, health economists, programmers and trial managers. The two consultant surgeons have considerable experience in the design and conduct of RCTs and they currently hold an NIHR grant investigating other forms of haemorrhoidal surgery (HTA 08/24/02: the eTHoS study). All three surgeons have experience of surgical techniques for the management of haemorrhoids including both HAL and RBL.

- Steven Brown is Principle Investigator(PI) and grant holder for the ISAAC trial (CRUK/08/038: comparison of surgery or chemotherapy for advanced colorectal cancer) and the eTHoS trial (HTA 08/24/02: comparison of conventional haemorrhoidectomy versus stapled anopexy for haemorrhoids). He is the UK Chief Investigator for the Libertas trial (Phase II assessment of Methoxamine for the treatment of faecal incontinence), PI for the CREST trial (CRUK/08/005: stenting or surgery for obstructing bowel cancer), the CONFIDeNT trial (tibial neuromodulation for treatment of faecal incontinence) and the ULISES trial (investigation of Ulimorelin for the treatment of post-operative ileus). He is also an independent expert on the DMEC panel for the FIAT trial (HTA 07/89/01: Fistula plug versus flap for fistula in ano).
- Angus Watson is Chief Investigator of the eTHoS trial (HTA 08/24/02). He has just been awarded an Honorary Chair in Colorectal Surgery from the University of Stirling. He is a Chief Investigator of a European-wide multicentre RCT comparing biological mesh versus standard surgical treatment for dehisced abdominal wounds: the STAR study. He is a PI for CREST and FIAT. He has three clinical fellows studying the utility of metabolomics in the discovery of disease biomarkers. He designed and ran a single site RCT comparing stapled surgery v RBL.
- James Tiernan is a Specialist Registrar in General Surgery in the Yorkshire Deanery and is currently undertaking a CRUK Clinical Research Fellowship.
- Daniel Hind is Assistant Director of the Sheffield CTRU which is currently supporting the delivery of ten randomised controlled trials, all of which are funded through either MRC or NIHR research programmes including six through the HTA programme. Three are clinical trials of investigational medicinal products; two are medical device studies. He is a former HTA grant holder (06/70/01: Chemoprevention of colorectal cancer) and currently holds grants from another NIHR programme (PHR 09/3004/01) and the MRC (G1001406).
- Mike Bradburn is a senior statistician at Sheffield CTRU and currently provides statistical oversight for three studies funded by the HTA (06/01/02; 08/64/01; 08/107/01).
- Allan Wailoo is Reader in Health Economics in the School of Health and Related Research (SchARR) at the University of Sheffield, Director of the National Institute for Health and Clinical Excellence (NICE) Decision Support Unit, and a current NIHR grant holder (08/64/01).
- Neil Shephard is a statistician employed jointly at Sheffield CTRU and the NIHR Yorkshire & Humber Research Design Service.

- Katie Biggs is a Research Associate in the Sheffield CTRU, she has worked as a Study Manager for an NIHR portfolio adopted study funded by Shire Pharmaceuticals and a Trial Co-ordinator for a HTA funded randomised controlled trial (The 3Mg Trial: 06/01/02).

9. Ethical Issues

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

The trial documentation, including this protocol, has been submitted to South Yorkshire Research Ethics Committee (REC). The patient information leaflet, patient consent form, and any other patient facing documentation are included in the ethics application.

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

The management of symptomatic haemorrhoids is generally dictated by a combination of patient choice, surgeon's preference and local expertise, experience and facilities. The emergence of HAL has further added to the management dilemma. There is a genuine lack of high quality evidence comparing HAL with established techniques, as shown in the recent NICE overview, which this trial aims to rectify. As such, in cases of second and third degree haemorrhoids there is true clinical equipoise regarding the best management. Both treatments are standard practice for this group of patients.

10. Involvement of Service Users

We are committed to involving service users at each stage of our research, from design to dissemination. From our patient and public consultation event, we have identified an individual who is willing to join the grant application team. They will attend the six-monthly Trial Steering Committee meetings. We have had input from service users in regards to the study design, including some of the patient questionnaires and the length of follow-up involved and we have sought the TSC member's opinion on study documents submitted to the REC.

11. Methods of Dissemination of Results

We expect several manuscripts prepared from this research to be published in high impact peer-reviewed journals, including publication of this protocol itself. We will publish the results and a lay summary on the study website upon study completion.

The results will enable clinicians to provide patients with up-to-date, robust information so that they can make an informed choice of the treatment option most appropriate to their individual needs. Our findings will be disseminated through the Association of Coloproctology of Great Britain and Ireland. This professional society represents over 1000 colorectal specialists. The objectives of the

association are to advance the science and practice of coloproctology; advance, educate and promote standards, training and other matters relating to best clinical practice in coloproctology amongst members of the medical profession; provide and disseminate information to health care professionals and members of the public on matters relating to coloproctology; and to promote high ethical standards. The trial will involve up to 14 colorectal surgical units from across the UK who will be involved in the NIHR research process. Some are already NIHR investigators and therefore directly contribute to the NIHR faculty and it is hoped that others will be future investigators.

12. Costing the project

12.1 Service support costs (research nurses)

12.1.1 Year One (Recruitment): est. 01 Oct 2012 – 30 Sep 2013

The research team will negotiate 12 month research nurse posts with 12-14 individual trusts. The research grant will cover 0.3 WTE of a research nurse up to the top of *Agenda for Change* Band 6 over these 12 months (est. £13,615 between 01 Oct 12 to 30 Sep 13).

As recruitment activity would constitute the great majority of the work we are looking to the CLRNs to make up this contract to as much of a full time post as possible (factors affecting recruitment are detailed below). At the time of writing, most Comprehensive Local Research Networks (CLRNs) are committing 0.7 WTE per centre as a service support costs under HSG (97)32 (Responsibilities for meeting patient care costs associated with research and development in the NHS).

This will allow recruitment of 12-14 centres, each tasked with recruiting a minimum of 40 participants (assuming 4-6 centres will sign up but not contribute to recruitment) and still leave funding for follow-up.

There may be additional sites willing to support the trial in their trust without receiving this payment in year one. This will be up to the individual trusts and will be discussed on a case by case basis with the CI, Sponsor and Trial Manager.

12.1.2 Year Two (Follow-up): est. 01 Oct 2013 – 30 Sep 2014

At the start of Year 2, the number of participants who require 12 month follow-up at each trust will be known. The research team would offer the CLRNs (this may have to be contracted via the trust) £300 per patient recruited in Year 1 for the purposes of 12 month follow-up (postage of questionnaires to patient and GP, a half hour telephone interview with participants, and completion of CRFs from hospital notes) and closeout visit, plus support for any monitoring activity required (likely to be zero or one three hour visit).

This has been agreed by the lead CLRN (South Yorkshire), Cheshire & Merseyside CLRN and West Midlands (South) CLRN and we will seek agreement for other CLRNs when approached.

12.2 Treatment costs (cost of the procedures)

No additional costs compared to standard care.

The Research Accountant from STH, the lead organisation, has confirmed that there will be no excess treatment costs arising from participation in the study as trusts already support considerable numbers of each procedure and block randomisation by centre will ensure that there are no local imbalances in treatment type.

13. Funding Source

This trial is funded by the NIHR Health Technology Assessment (HTA) programme.

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Protocol amendments since initial REC approval

Version number	Changes made	Date of REC approval	Amendment number
2.0	Adverse event details amended; 6.9.1, page 17	30/07/2012	Substantial amendment 1
2.1	Amended protocol to allow 'Delegated site	13/08/2012	Minor

	staff' to take consent, previously only research nurses were listed as able to take consent; 6.1, page 8		amendment 2
3.0	Clarified that only related adverse events and serious adverse events will be recorded; 6.9, page 17	30/08/2012	Substantial amendment 2
4.0	Added patients with hypocoagulability disorders to exclusion criteria	24/10/2012	Substantial amendment 3
5.0	Changed the collection of baseline data from the point of randomisation to the day of allocated treatment; 6.4.4, page 13 and 6.10, Table 1, page 18. Flow chart amended; 6.4.3, page 12	07/02/2013	Substantial Amendment 6
5.1	Made a further amendment to the secondary outcomes; missed in version 5.0; 6.4.2, page 11.	07/03/2013	Minor Amendment 5
6.0	Removed inclusion criterion 'Either presenting for the first time or after one failure of RBL' and added three exclusion criteria: 'Patients that have had previous surgery for haemorrhoids (at any time)', 'Patients that have had injection therapy for haemorrhoids in the past 3 years' and 'Patients that have had more than one RBL procedure in the past 3 years'; 6.6, page 13.	25/03/2013	Substantial Amendment 7
7.0	Added: 'patients will have a minimum of 24 hours to decide whether they wish to take part' for clarification; 6.1, page 8.	30/04/2013	Substantial Amendment 8
8.0	Added a participant questionnaire to be completed prior to randomisation. Added 'Continence questionnaire' in 6.4.4. to the list of items measured in the six week follow-up (in line with 6.4.2 and 6.4.3); 6.4.2-6.4.4, pages 11-13 Addition of a paragraph to account for new sites that will not receive funding from the research grant in year 1; 12.1.1, page 22	05/07/2013	Substantial Amendment 9