The HubBLe Trial: haemorrhoidal artery ligation (HAL) versus rubber band ligation (RBL) for symptomatic second- and third-degree haemorrhoids: a multicentre randomised controlled trial and health-economic evaluation

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NHS

National Institute for Health Research

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This report

Abstract

The HubBLe Trial: haemorrhoidal artery ligation (HAL) versus rubber band ligation (RBL) for symptomatic second- and third-degree haemorrhoids: a multicentre randomised controlled trial and health-economic evaluation

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Background: Optimal surgical intervention for low-grade haemorrhoids is unknown. Rubber band ligation (RBL) is probably the most common intervention. Haemorrhoidal artery ligation (HAL) is a novel alternative that may be more efficacious.

Objective: The comparison of HAL with RBL for the treatment of grade II/III haemorrhoids.

Design: A multicentre, parallel-group randomised controlled trial.

Perspective: UK NHS and Personal Social Services.

Setting: 17 NHS Trusts.

Participants: Patients aged ≥ 18 years presenting with grade II/III (second- and third-degree) haemorrhoids, including those who have undergone previous RBL.

Interventions: HAL with Doppler probe compared with RBL.

Outcomes: Primary outcome – recurrence at 1 year post procedure; secondary outcomes – recurrence at 6 weeks; haemorrhoid severity score; European Quality of Life-5 Dimensions, 5-level version (EQ-5D-5L); Vaizey incontinence score; pain assessment; complications; and cost-effectiveness.

Results: A total of 370 participants entered the trial. At 1 year post procedure, 30% of the HAL group had evidence of recurrence compared with 49% after RBL [adjusted odds ratio (OR) = 2.23, 95% confidence interval (CI) 1.42 to 3.51; $p = 0.0005$]. The main reason for the difference was the number of extra procedures required to achieve improvement/cure. If a single HAL is compared with multiple RBLs then only 37.5% recurred in the RBL arm (adjusted OR 1.35, 95% CI 0.85 to 2.15; $p = 0.20$). Persistence of significant symptoms at 6 weeks was lower in both arms than at 1 year (9% HAL and 29% RBL), suggesting significant deterioration in both groups over the year. Symptom score, EQ-5D-5L and Vaizey score improved in both groups compared with baseline, but there was no difference between interventions. Pain was less severe and of shorter duration in the RBL group; most of the HAL group who had pain had mild to moderate pain, resolving by 3 weeks. Complications were low frequency and not significantly different between groups. It appeared that HAL was not cost-effective compared with RBL. In the base-case analysis, the difference in mean total costs was £1027 higher for HAL. Quality-adjusted life-years (QALYs) were higher for HAL; however, the difference was very small (0.01) resulting in an incremental cost-effectiveness ratio of £104,427 per additional QALY.

Conclusions: At 1 year, although HAL resulted in fewer recurrences, recurrence was similar to repeat RBL. Symptom scores, complications, EQ-5D-5L and continence score were no different, and patients had more pain in the early postoperative period after HAL. HAL is more expensive and unlikely to be cost-effective in terms of incremental cost per QALY.

Limitations: Blinding of participants and site staff was not possible.

Future work: The incidence of recurrence may continue to increase with time. Further follow-up would add to the evidence regarding long-term clinical effectiveness and cost-effectiveness. The polysymptomatic nature of haemorrhoidal disease requires a validated scoring system, and the data from this trial will allow further assessment of validity of such a system. These data add to the literature regarding treatment of grade II/III haemorrhoids. The results dovetail with results from the eTHoS study [Watson AJM, Hudson J, Wood J, Kilonzo M, Brown SR, McDonald A, *et al.* Comparison of stapled haemorrhoidopexy with traditional excisional surgery for haemorrhoidal disease (eTHoS): a pragmatic, multicentre, randomised controlled trial. *Lancet* 2016, in press.] comparing stapled haemorrhoidectomy with excisional haemorrhoidectomy. Combined results will allow expansion of analysis, allowing surgeons to tailor their treatment options to individual patients.

Trial registration: Current Controlled Trials ISRCTN41394716.

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List of abbreviations

AMI	Agency for Medical Innovations		NMB	net monetary benefit
BMI	body mass index		NSAID	non-steroidal anti-inflammatory drug
BNF	*British National Formulary*		OH	open haemorrhoidectomy
CEA	cost-effectiveness analysis		OR	odds ratio
CEAC	cost-effectiveness acceptability curve		PP	per protocol
CI	confidence interval		PPI	patient and public involvement
CRF	case report form		PSA	probabilistic sensitivity analysis
CTRU	Clinical Trials Research Unit		PSSRU	Personal Social Services Research Unit
CUA	cost–utility analysis		QALY	quality-adjusted life-year
DMEC	Data Monitoring and Ethics Committee		QoL	quality of life
EH	excisional haemorrhoidectomy		RBL	rubber band ligation
EQ-5D	European Quality of Life-5 Dimensions		RCT	randomised controlled trial
			REC	Research Ethics Committee
EQ-5D-5L	European Quality of Life-5 Dimensions (5-level version)		SAE	serious adverse event
			ScHARR	Sheffield School of Health and Related Research
GP	general practitioner		SD	standard deviation
HAL	haemorrhoidal artery ligation		SE	standard error
HALO	haemorrhoidal artery ligation operation		SH	stapled haemorrhoidopexy
HRG	Healthcare Resource Group		SOPC	surgical outpatient clinic
HRQoL	health-related quality of life		STH	Sheffield Teaching Hospitals
ICC	intraclass correlation		SUR	seemingly unrelated regression
ICER	incremental cost-effectiveness ratio		THD	transanal haemorrhoidal dearterialisation
IQR	interquartile range			
ITT	intention to treat		TSC	Trial Steering Committee
NICE	National Institute for Health and Clinical Excellence		VAS	visual analogue scale

Plain English summary

Background

There are many treatments for piles (haemorrhoids). In less-severe cases, one treatment is rubber band ligation (RBL), which involves placing a small band around the base of the pile to cut off the blood supply. RBL is a relatively painless outpatient treatment with minimal complications but recurrence is common. Haemorrhoidal artery ligation (HAL) uses a device to locate the arteries feeding the piles, which are then stitched. This procedure takes longer and is more painful but may reduce recurrence. We compared these two procedures to see which was best.

Results

One year after surgery, 49% of the patients had a recurrence of symptoms after RBL compared with 30% of patients undergoing HAL. About one-third of RBL patients, whose symptoms persisted, underwent a further surgical procedure, many having repeated RBL. If patients having further RBL are considered as having a 'course' of therapy then there was minimal difference between the treatments. Most patients initially felt better after surgery, but symptoms returned within the year. Symptom scores, quality of life, continence and complications were similar after both procedures. Those undergoing HAL tended to have more pain but the discomfort was not severe in the majority of patients and resolved by 1–3 weeks after the operation. HAL is much more expensive.

Conclusion

Haemorrhoidal artery ligation reduced recurrence compared with RBL, but these RBL recurrences can often be treated successfully by simple re-banding. A course of RBL, therefore, has similar recurrence rates to HAL. HAL is also more painful in the short term, waiting time is longer and it is more expensive.

Scientific summary

Background

Anal cushions are a normal component of the anal canal and are composed predominantly of vascular tissue, supported by smooth muscle and connective tissue. Pathological changes in the anal cushions with enlargement of the vascular plexus result in haemorrhoidal development. Haemorrhoids are common, affecting as many as 1 in 3 of the population, and result in a significant burden to the UK NHS. Over 20,000 haemorrhoidal operations are carried out in England each year. 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 anaesthetic. Although RBL is cheap, it has a high recurrence rate and often needs repeating. Failure may require surgical intervention, commonly the traditional 'open' haemorrhoidectomy (OH) or a stapled haemorrhoidopexy (SH), both requiring anaesthetic. OH is associated with considerable postoperative discomfort and a delay in return to normal activity, but has a low recurrence rate. SH has a slightly higher recurrence rate, but potentially shorter recovery. An alternative treatment is haemorrhoidal artery ligation (HAL), which, although it also requires an anaesthetic, is thought to enable an even quicker return to normal activity. Recurrence rates are reportedly similar to SH, but complication rates are lower.

There are substantial data in the literature concerning the efficacy and safety of RBL, including multiple comparisons with other interventions. Recurrence varies from 11% to > 50%, the broad range probably reflecting the definition of recurrence, severity of the disease, number of treatments and/or the intensity and length of follow-up. In most studies, the incidence of recurrence is > 30% and appears greatest for grade III (third-degree) haemorrhoids (prolapsing piles requiring manual reduction). Significant complications are rare after RBL.

Although HAL requires an anaesthetic, evidence suggests a recovery that is similar to RBL, but an effectiveness that approaches the more intensive surgical options. There are significant data about the effectiveness of HAL, including four systematic reviews, 11 randomised controlled trials (RCTs), seven non-randomised trials and > 60 case series. All of these reviews highlight the lack of good-quality data as evidence for the advantages of the technique. There are no existing RCTs that compare HAL with RBL.

Objectives

The aim of this study was to establish the clinical effectiveness and cost-effectiveness of HAL compared with conventional RBL in the treatment of people with symptomatic prolapsing haemorrhoids (second or third degree).

The primary objective was to compare patient-reported symptom recurrence at 12 months following the procedure. Recurrence was defined using a simple dichotomous outcome that was derived from a previously published systematic review, and supplemented with general practitioner (GP) and hospital notes.

The secondary objectives were to compare postoperative:

- symptom severity score
- health-related quality of life [using the European Quality of Life-5 Dimensions (EQ-5D)]

- continence (using the validated Vaizey incontinence score)
- pain [using a 10-cm visual analogue scale (VAS)]
- surgical complications
- need for further treatment
- clinical appearance of haemorrhoids at proctoscopy following recurrence
- health-care costs
- cost-effectiveness.

Methods

This was a multicentre, parallel-group RCT involving 18 centres throughout England and Scotland. Delegated study staff located at individual centres identified and consented potential participants.

These participants fell into two basic groups:

1. Patients presenting to the surgical outpatient clinic (SOPC) with symptomatic haemorrhoids, for which alternative diagnoses had been excluded either clinically or after investigation.
2. Patients with symptoms – due to haemorrhoids – confirmed, who returned to SOPC following one unsuccessful RBL.

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

Sheffield Clinical Trials Research Unit (CTRU) coordinated follow-up and data collection in collaboration with the UK centres. Participant study data were collected and recorded on study-specific case report forms and patient questionnaires, and then entered on to a web-based data capture system, transferring data to Sheffield CTRU for analysis.

Data were collected to establish which patients had further treatment for recurrent symptoms or complications following their initial procedure. This was achieved at a clinic visit around 6 weeks following the intervention and by reviewing hospital records, asking the patients' consultants, writing to patients' GPs and questioning the patient via telephone interview at 12 months.

Setting

Sheffield Teaching Hospitals NHS Foundation Trust was the 'clinical coordinating centre' housing the Chief Investigator. A further 17 centres screened patients and delivered the trial; one centre did not recruit, so 17 centres recruited participants. Recruitment took place in outpatient clinics, RBL took place in outpatient clinics or theatre (depending on the Trust's current practice) and HAL took place in theatre.

Participants

The target population was patients who were referred to collaborating centres for treatment of haemorrhoids.

Inclusion criteria

- Adults aged ≥ 18 years with symptomatic second- or third-degree (grade II/III) haemorrhoids.

Exclusion criteria

- Patients who have had previous surgery for haemorrhoids (at any time).
- Patients who have had more than one injection treatment for haemorrhoids in the past 3 years.
- Patients who have had more than one RBL procedure in the past 3 years.
- Patients with known perianal sepsis, inflammatory bowel disease, colorectal malignancy or pre-existing sphincter injury.
- Patients with an immunodeficiency.
- Patients who were unable to have general or spinal anaesthetic.
- Patients who were currently taking warfarin or clopidogrel bisulfate (clopidogrel) or who had any other hypocoagulability condition.
- Patients who were currently taking nicorandil.
- Pregnant women.
- Patients who were unable to give full informed consent (this may be because of mental capacity or language barriers).
- Patients who were previously randomised to this trial.

Sample size

We assumed that the proportion of patients who experience recurrence following RBL was 30% and following HAL 15%. Therefore, the sample size required to detect a difference in recurrence rates with an odds ratio (OR) of '2', with 80% power and 5% significance, was 121 individuals per group. In order to account for any between-surgeon variation and loss to follow-up, we increased this to 175 per group.

Interventions

The intervention was either RBL or HAL – both established and well-documented procedures, considered as standard care by the National Institute for Health and Clinical Excellence.

Rubber band ligation is a basic surgical skill with which all senior staff are familiar and are competent in performing.

Haemorrhoidal artery ligation is a simple procedure that uses existing surgical skills and has a short learning curve. All of the surgeons involved in the study had completed the required training and, in addition, had carried out the manufacturer's recommendation of five procedures before commencing the study.

Statistical and health-economic analyses

Differences in the primary outcome of recurrence were analysed using logistic regression, adjusting for gender, age and history of previous intervention as fixed effect covariates and surgeon as a random effect. This allows the calculation of ORs with confidence intervals (CIs) for the effect of RBL relative to HAL, adjusting for the effects of covariates and the clustering by surgeon. The secondary outcomes of pain, symptoms and incontinence were analysed at each time point using a random-effects, generalised least squares model, adjusting for the same covariates. Procedural complications and serious adverse events (SAEs) were summarised as numbers and percentages.

A full economic evaluation, focusing on estimating the incremental cost per quality-adjusted life-year (QALY) of HAL compared with RBL over the 12-month follow-up period, was also carried out. A secondary cost-effectiveness analysis (CEA) was performed in terms of the incremental cost per recurrence avoided. Long-term cost-effectiveness was estimated by extrapolating the analyses beyond the trial time horizon.

Results

In total, 372 participants were randomly assigned to receive RBL or HAL; 187 patients were allocated to receive RBL, and 185 were allocated to receive HAL. Two of these participants (both randomised to RBL) were removed from the trial completely, as they were ineligible at the time of consent, and, therefore, a total of 370 participants were entered into the trial. The recurrence rate for HAL was significantly lower than for RBL at 12 months (30% vs. 49%, adjusted OR = 2.23, 95% CI 1.42 to 3.51; $p = 0.0005$). Further treatment was required in 31% of the RBL group and 15% of the HAL group (adjusted OR for further procedure = 2.86, 95% CI 1.65 to 4.93; $p = 0.0002$). Eighteen per cent of the RBL group received a second banding session within the year. In these cases, because the initial haemorrhoids were incompletely treated, excluding these RBLs as recurrence resulted in a larger reduction of our recurrence rate for RBL and no statistical difference between the groups (HAL 30% vs. RBL 37.5%, adjusted OR 1.35, CI 0.85 to 2.15; $p = 0.20$).

At 6 weeks following the procedure, 13 (9%) of patients in the HAL group and 44 (29%) of patients in the RBL group reported their haemorrhoidal symptoms as 'unchanged' or 'worse' (adjusted OR 4.35, 95% CI 2.19 to 8.65; $p < 0.001$).

The haemorrhoid symptom severity score improved in both arms compared with scores prior to procedure. At 6 weeks, the mean scores reduced from 6.5 [standard deviation (SD) 3.3] to 4.0 (SD 3.5) for RBL and from 6.4 (SD 3.0) to 3.0 (SD 3.1) for HAL. There was a statistically significant difference between groups at 6 weeks in favour of HAL (adjusted mean difference 1.0, 95% CI 0.3 to 1.8; $p = 0.01$) but no difference was apparent at 1 year (difference in means 0.0, 95% CI –0.8 to 0.8; $p = 0.98$). Applying the definition used by Nyström *et al.*, in which a score of 0 or 1 points indicates symptomatic cure, the two interventions were similar at both 6 weeks (HAL 38% vs. RBL 31%; adjusted OR 0.73, 95% CI 0.44 to 1.22; $p = 0.23$) and 1 year (HAL 31% vs. RBL 27%; adjusted OR 0.79, 95% CI 0.46 to 1.38; $p = 0.42$) (Nyström PO, Qvist N, Raahave D, Lindsey I, Mortensen N. Randomized clinical trial of symptom control after stapled anopexy or diathermy excision for haemorrhoid prolapse. *Br J Surg* 2010;**97**:167–76).

Haemorrhoidal artery ligation was associated with a short-term reduction in mean health utility (European Quality of Life-5 Dimensions, 5-level version) at 1 and 7 days postoperatively, whereas for RBL the mean had reverted back at 1 week. The adjusted difference in means were 0.08 (95% CI 0.04 to 0.13; $p = 0.001$) at 1 day and 0.08 (95% CI 0.05 to 0.12; $p = 0.001$) at 7 days in favour of RBL. The two arms were similar (and above baseline values) at all time points from day 21 onwards.

There was a small reduction of about 1–2 points in the mean Vaizey faecal incontinence score 6 weeks after both interventions. There was no evidence of a difference in incontinence score between the two interventions. The majority of patients reported increased pain, measured by VAS, following both procedures (56% RBL vs. 71% HAL). For RBL, this pain was usually of low intensity (median VAS score on day 1: 3.0) and resolved rapidly to below baseline values (median VAS score on day 7: 1.0); about 50% of patients required analgesics for the first few days after treatment. For HAL, the pain was significantly greater, with moderate pain at day 1 (median VAS score 5.0, mean difference from RBL –1.2, 95% CI –1.8 to –0.5; $p < 0.001$) and mild pain on day 7 post procedure (median VAS score 3.0, mean difference from RBL –1.5, 95% CI –2.0 to –1.0; $p < 0.001$). Pain had resolved in almost all patients by the 3-week assessment (median VAS score 0.0 RBL vs. 1.0 HAL, mean difference from RBL –0.1, 95% CI –0.6 to 0.3; $p = 0.44$). Analgesia was required by the majority after a HAL procedure on a daily basis for the first week, but tailed off such that at 3 weeks 72% of patients had stopped taking medication.

Twelve patients (7%) reported a SAE (in all cases entailing hospitalisation) following HAL procedure, compared with two (1%) in the RBL arm. In the HAL arm there were six admissions due to pain, two for urine retention, and one each of bleeding, wound infection, nausea/vomiting and a reaction to anaesthetic. For RBL, both events related to prolonged hospitalisation: one for severe pain and one for bleeding 12 days following banding.

The main findings of within-trial cost–utility analysis suggest that HAL procedure appeared not to be cost-effective compared with RBL at a cost-effectiveness threshold of £20,000–30,000 per QALY. In the base-case results, the difference in mean total costs was £1027 higher for HAL than RBL. QALYs were higher for HAL; however, the difference was very small (0.01), resulting in an incremental cost-effectiveness ratio (ICER) of £104,427 per additional QALY. At the threshold of £20,000 per QALY, HAL has zero probability of being cost-effective; at the threshold of £30,000, it has 0.05 probability of being cost-effective.

The base-case CEA suggests that the incremental cost per recurrence avoided was estimated as £4882. In a sensitivity analysis scenario using recurrence from the consultant questionnaire only, the incremental cost per recurrence was estimated as £6346. The extrapolation for 3 years beyond the trial time horizon generated an ICER of £21,887 per QALY, and HAL has 0.34 probability of cost-effectiveness.

Conclusions

Haemorrhoidal artery ligation is a more clinically effective procedure than a single RBL intervention. However, if HAL is compared with repeat RBL the procedures become equivalent in terms of recurrence. Similarly, symptom severity score, complications, quality of life and continence score were no different between interventions, and patients had more pain in the early postoperative period after a HAL procedure. The HAL procedure is significantly more expensive than RBL and not cost-effective in terms of cost per QALY.

Trial registration

This trial is registered as ISRCTN41394716 (UKCRN database ID 12486).

Funding

Chapter 1 Introduction

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.[1]

Approximately 23,000 haemorrhoidal operations were carried out in England in 2004–5,[2] 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.[3] Although there are some variations [such as LigaSure® (Covidien – Medtronic, Minneapolis, MN, USA) haemorrhoidectomy], surgery is commonly traditional 'open' haemorrhoidectomy (OH) or a stapled haemorrhoidopexy (SH); both require an anaesthetic. OH is associated with considerable postoperative discomfort, sometimes necessitating an 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.[4] 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.[5]

There are substantial data in the literature concerning the efficacy and safety of RBL, including multiple comparisons with other interventions.[6–12] Recurrence varies from 11% to > 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, unreducible prolapse), the number of treatments and/or the intensity and length of follow-up. In most studies, the incidence of recurrence is > 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%[3]), bleeding (3–4%, sometimes necessitating further treatment[9]) and vasovagal symptoms (3%[13]). There have also been rare incidences of blood transfusion[3,11,14–18] and severe pelvic sepsis, with a few instances leading to death.[13] 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 include four systematic reviews,[5,19–21] 11 randomised controlled trials (RCTs),[22–32] seven non-randomised trials[33–39] and > 60 case series. An 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;[40] this is summarised below.

- In terms of efficacy, studies with > 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, postoperative haemorrhage requiring intervention (readmission, transfusion, reoperation or correction of coagulopathy) was reported in < 1.2%, haemorrhoidal thrombosis was seen in < 3.5% of patients and fissure formation in < 2.1%.

- The data from the three RCTs comparing HAL with SH and OH are difficult to combine, but efficacy seems similar for all of the 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 postoperative pain and longest recovery. There are conflicting results as to whether or not 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 used.

Rationale

Both of the systematic reviews and the NICE overview highlight the lack of good-quality data as evidence for the advantages of the technique; most data are from case series. Even the numerous RCTs have significant methodological drawbacks that make them subject to selection, performance, attrition and detection bias. Indeed, none of the studies is powered to reach any meaningful conclusion. There are no existing RCTs that compare HAL with RBL, although there is now one non-randomised comparison with small numbers of patients.[41]

Research objectives

The HubBLe study aimed to establish the clinical effectiveness and cost-effectiveness of HAL compared with conventional RBL in the treatment of people with symptomatic second- or third-degree (grade II or grade III) haemorrhoids.

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

The secondary objectives were to compare postoperative:

- symptom severity score (adapted from Nyström *et al*.[42])
- health-related quality of life [HRQoL; using the European Quality of Life-5 Dimensions (EQ-5D)[43]]
- continence (using the validated Vaizey incontinence score[44])
- pain [using a 10-cm visual analogue scale (VAS)]
- surgical complications
- need for further treatment
- clinical appearance of haemorrhoids at proctoscopy following recurrence
- health-care costs
- cost-effectiveness.

Text reproduction

The findings of this trial have been published in *The Lancet* and as such there is reproduced text on pp. 24–26 of *The Lancet* publication.[45]

Chapter 2 Methods

This report is concordant with the Consolidated Standards of Reporting Trials (CONSORT) statement (2010).[46]

Trial design

We undertook a multicentre, parallel-group RCT of HAL compared with conventional RBL in the treatment of people with symptomatic second- or third-degree (grade II or grade III) haemorrhoids in 17 NHS Trusts in the UK. Participants were individually randomised to HAL or RBL, in equal proportion at all centres.

Important changes to methods after trial commencement

Recruitment commenced on 12 November 2012, and, following this, in response to early observations, a number of changes were made to the protocol (see *Appendix 1*) and trial methods. Between the initial Research Ethics Committee (REC) approval and study commencement, there were two substantial amendments clarifying the serious adverse event (SAE) reporting and the expected adverse events. The protocol was published in *BMC Gastroenterology* in October 2012.[47]

In October 2012 (substantial amendment 3; protocol version 4.0), a change was made to the eligibility criteria to exclude patients with hypercoagulability disorders [in addition to those on warfarin or clopidogrel bisulfate (clopidogrel)] following a request from one of the Principal Investigators during a site set-up visit.

In January 2013 (substantial amendment 6; protocol version 5.0), the baseline data collection was changed to the day of surgery, rather than at randomisation. Sites and treatment arms differed in the time between randomisation and treatment, and this change was made to standardise the data collection as much as possible. This also standardised the time between the baseline and the 12-month follow-up, as the follow-up time point was based on the date of trial treatment.

In March 2013 (substantial amendment 7; protocol version 6.0), we removed one inclusion criterion and replaced it with three exclusion criteria for clarification. The inclusion criterion 'Either presenting for the first time or after failure of one banding' at sites had caused some confusion at sites and it was also decided during the review of this criterion that patients with some historical treatments for haemorrhoids could be included.

The study team, the sponsor and the Trial Steering Committee (TSC) discussed the windows in which treatment is clinically relevant, and agreed that there should be a difference between surgical and non-surgical treatment for haemorrhoids (and that dietary advice would not exclude patients). The amended criteria clarified that all previous surgery for haemorrhoids and more than one injection treatment or banding in the previous 3 years would lead to exclusion. For non-surgical treatments, > 3 years was considered a historical event and therefore not relevant to the current research. As one previous banding was allowed within the protocol, this was also the case for injection treatments, as they were both non-surgical; one previous course of injection treatment would not mean that patients were excluded.

In April 2013 (substantial amendment 8; protocol version 7.0), we added 'patients will have at least 24 hours to decide whether to take part' to the protocol, in order to provide clarification, as it was not explicitly stated previously. The 24-hour period was an appropriate time frame for the study population and intervention.

A pre-randomisation questionnaire was introduced in July 2013 (substantial amendment 9; protocol version 8.0). The Data Monitoring and Ethics Committee (DMEC) suggested that patient-reported

outcomes can be affected by the knowledge of their allocation. As baseline data collection took place on the day of surgery (following Substantial Amendment 6), the majority of patients knew their allocation by this point; the concern was that perceived pain and quality of life (QoL) may differ between the groups due to expectation bias at this time,[48] even though no procedure had yet taken place. The senior trial statistician reported that the early data did indeed support this hypothesis, in particular with higher self-reported symptoms in the HAL arm. As a result of this, the protocol was amended to incorporate a questionnaire to be completed before randomisation.

To improve the questionnaire completion rates at the 12-month follow-up, we introduced a prize draw for participants who returned the questionnaires in February 2014 (substantial amendment 7; no change to protocol). We completed three draws of £50 each.

Owing to the long waiting times for the HAL procedure, the dropout rate prior to the procedure was higher than expected. To account for this attrition, in April 2014 (substantial amendment 12; no change to protocol) the recruitment target was increased to 370 in order to achieve the sample size of 350 prior to treatment.

Participants and eligibility criteria

The trial was coordinated from the Clinical Trials Research Unit (CTRU) in the Sheffield School of Health and Related Research (ScHARR). Delegated study staff located at individual centres identified and consented potential participants.

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

Potential participants fell into three groups:

1. Patients presenting to the surgical outpatient clinic (SOPC) with symptomatic haemorrhoids that did not require further tests: this group was identified by the clinical team from the general practitioner (GP) referral letter and a patient information sheet was sent to them prior to their clinic appointment. If they were willing to participate then they were consented and randomised when they attended the appointment.
2. Patients presenting to the SOPC with symptomatic haemorrhoids that required further tests to exclude other diagnoses: this group were identified by the clinician at the clinic appointment and given a patient information sheet. They underwent the necessary outpatient tests (usually endoscopy) and, if negative (i.e. the symptoms are due to haemorrhoids), they were contacted by the research nurse prior to attending their follow-up clinic appointment. They were then randomised and consented when they reattended the clinic.
3. Patients who returned to SOPC following one unsuccessful RBL: they were identified by the clinician at their first clinic appointment (when they have RBL) and given a patient information sheet. They were contacted prior to a follow-up appointment (usually 6 weeks after treatment) by a research nurse. If they remained symptomatic and were willing to participate, they were consented and randomised when they reattended.

All potential participants had a minimum of 24 hours in which to decide whether or not they wished to take part. Patients with investigations excluding pathologies other than haemorrhoids, and all of those who had undergone RBL, were contacted by the research nurse before the planned follow-up clinic to ascertain whether or not they met entry criteria and were interested in entering the trial. They would then be seen by the consultant and research nurse in clinic where recruitment and randomisation took place.

Potential participants were invited to take part in the trial if they were aged ≥ 18 years and had symptomatic second- or third-degree haemorrhoids.

Patients were excluded if they met any of the following criteria:

- have had previous surgery for haemorrhoids (at any time)
- have had more than one injection treatment for haemorrhoids in the past 3 years
- have had more than one RBL procedure in the past 3 years
- with known perianal sepsis, inflammatory bowel disease, colorectal malignancy, pre-existing sphincter injury
- with an immunodeficiency
- unable to have general or spinal anaesthetic
- currently taking warfarin, clopidogrel or have any other hypercoagulability condition
- pregnant women
- unable to give full informed consent (this may be due to mental capacity or language barriers)
- previously randomised to this trial.

Settings and locations where the data were collected

The CTRU coordinated the follow-up and data collection in collaboration with centres. Participant study data were collected and recorded on study-specific case report forms (CRFs) by centre research staff, and then entered on to a remote web-based data capture system at site. To improve the rate of completion, research nurses could complete the participant questionnaires with the participants at the visit or over the telephone, or the participants could return the questionnaires by post to the centres at all time points. Patient questionnaires, at 12 months, could also be completed online and could be returned to the CTRU by participants for data entry.

Interventions

Participants were randomised to receive either RBL or HAL. Both interventions are established and well-documented procedures, which are considered standard care by NICE.[40,49]

Conventional RBL uses a device that allows a rubber band to be applied to each haemorrhoid via a proctoscope. The device used across sites was a suction device (various manufacturers), but bands can be applied using a forceps ligator. This rubber band 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 Sheffield Teaching Hospitals (STH) highlighted that prior to the trial over 20 such procedures were carried out every week. The procedure is a basic surgical skill with which all senior staff are familiar and competent in performing. All surgeons involved in the study performed this procedure routinely.

Haemorrhoidal artery ligation uses a proctoscope that is modified to incorporate a Doppler transducer. There are two types of equipment in common use: the HALO (haemorrhoidal artery ligation operation) device [Agency for Medical Innovations (AMI) HAL Doppler system, CJ Medical, Truro, UK] and the THD (transanal haemorrhoidal dearterialisation) device (THD Lab, Correggio, Italy). Both devices operate on the same principle, essentially enabling accurate detection of the haemorrhoidal arteries feeding the haemorrhoidal cushions. Targeted ligation of the vessels with a suture reduces haemorrhoidal engorgement. When combined with a 'pexy' suture, both bleeding and haemorrhoidal prolapse are addressed. All of the surgeons participating in the trial ensured that the need for a pexy suture was routinely assessed and recorded. The procedure is simple, uses existing surgical skills and has a short learning curve, with the manufacturers recommending at least five mentored cases before independently practising. All of the surgeons involved in the study had completed this training prior to the start and, in addition, had carried out more than five procedures prior to delivering the study treatment.

Trial procedures were carried out as soon as possible after randomisation. RBL is a brief procedure, which, in many cases, can be carried out at the initial clinic visit. By contrast, HAL is an invasive procedure, usually performed under general anaesthetic, and requires a theatre admission, which may be some considerable time after assessment. The HubBle trial defined 'baseline' as being the date of procedure, and 'recurrence at 1 year' as being from this date onwards.

Outcomes

Measurement of outcomes

Following consent but prior to randomisation, a participant-completed questionnaire was administered which included questions relating to pain, symptoms, EQ-5D-5L (European Quality of Life-5 Dimensions, 5-level version), continence and use of pain medications. The research nurse completed a patient assessment form, which included demographics and details of the haemorrhoids, including previous treatment(s).

The same participant questionnaire was repeated at baseline, defined as the day of the procedure; in addition, the procedure details CRF was completed by the consultant or the research nurse.

Short-term outcome assessments were completed by participants either via return of a postal questionnaire or a telephone call with the research nurse at days 1, 7 and 21 post procedure. This covered EQ-5D-5L, pain and use of pain medication.

Data were collected 6 weeks following the procedure and again at 12 months following the procedure in order to establish which patients required further treatment for recurrent symptoms or complications. Participants attended a 6-week clinic visit following the intervention at which they were asked details regarding GP visits, hospital attendance or further treatment since the procedure; the baseline questionnaire was also repeated at this time. A clinical assessment was recorded wherein complications, SAEs and further treatment (planned or completed) were reported; the haemorrhoidal grade was recorded when it was clinically assessed. The clinician was also asked whether or not, in his/her opinion, the patient's symptoms were improved.

Twelve-month data were collected from three sources. Details of further procedures were obtained from hospitals (by reviewing hospital records and asking the patients' consultants), by contacting the patients' GPs and, finally, by questioning the patient via telephone interview or postal questionnaire at 12 months.

Primary outcome measure

The main research question of the study was to ascertain the 1-year incidence of recurrence following HAL or RBL. The primary outcome was defined as the proportion of patients with recurrent haemorrhoids at 12 months post procedure, as derived from the patient's self-reported assessment in combination with GP and hospital records.

The trial was a pragmatic design with a dichotomous outcome. As no validated patient-reported symptom score exists, we based our definition of recurrence on Shanmugam *et al.*'s systematic review[12] 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 simplified Shanmugam's criteria[12] 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?'

Patients were considered to have recurrent haemorrhoids when any of the following were recorded (as shown in *Figure 1*):

 i. 'Unchanged or worse compared with before starting treatment' at 12 months, as reported by the patient, *or*
 ii. Any subsequent procedure (RBL, HAL, THD, haemorrhoidectomy, haemorrhoidopexy, haemorrhoidal injection or other relevant procedure) over the 12 months, *or*
iii. Presence of any symptoms or events that strongly indicated recurrent haemorrhoids [among patients not meeting (i) or (ii), as adjudicated by two trial investigators (JT, SB) who were blinded to allocated treatment].
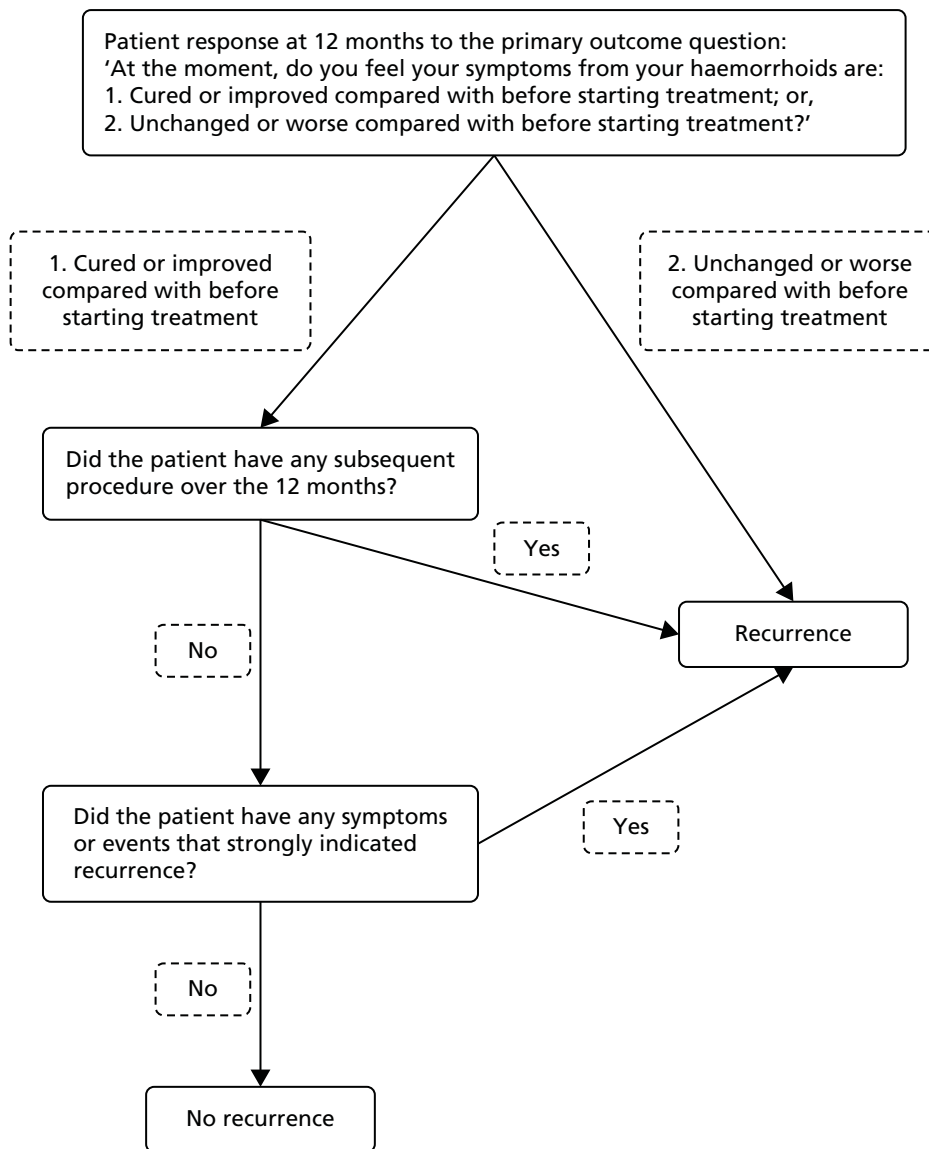
FIGURE 1 Decision tree for recurrence at 1 year.

Secondary outcome measures

Secondary end points seek to identify which treatment – HAL or RBL – is the most cost-effective, which is the least painful procedure with the fewest complications, and which has the greatest effect on the patient's QoL. Secondary end points are therefore:

- Persistence of significant symptoms defined analogously to the 12-month outcome.
- Symptom severity score (adapted from Nyström *et al.*[42]). This score is the sum of the scores from all five questions and is therefore a number on a nominal scale in the range of 0 to 15; where an increase in number is an increase in symptoms.
- HRQoL using the EQ-5D-5L.[43] A summary index with a maximum score of 1 can be derived from the five dimensions by conversion using a table of scores. The maximum score of 1 indicates the best health state, by contrast with the scores of the individual questions, where higher scores indicate more severe or frequent problems.
- Continence using the validated Vaizey incontinence score.[44] The Vaizey incontinence score is simply the sum of the scores from all of the seven questions, and is also a number on a nominal scale in the range of 0–24, for which an increase in number indicates more severe incontinence.
- Pain using a 10-cm VAS, for which '0' is 'no pain' and '10' is 'worst imaginable pain'.

- Surgical complications.
- Need for further treatment.
- Clinical appearance of haemorrhoids at proctoscopy following persistent symptoms at 6 weeks.
- Health-care costs/cost-effectiveness/quality-adjusted life-years (QALYs).

The schedule for collecting these end points is shown in *Table 1*.

Sample size

Assuming that the proportion of patients who experience recurrence following RBL is 30% and following HAL is 15%, the sample size calculated to detect a difference in recurrence rates with an odds ratio (OR) of 2 with 80% power and 5% significance was 121 individuals per group. In order to account for any between-surgeon variation and loss to follow-up, this was increased to 175 per group.

This increase was based on the conservative assumption that there would be 14 surgeons in the trial (one per centre, although the number of sites was increased) and intraclass correlation (ICC) of 2.5% in keeping with typical ICCs observed by Ukoumunne *et al.*[50] However, it was considered likely that each site would have a minimum of two surgeons, in which case the power to detect this difference was 85% (90% power if there was no between-surgeon variation). Because the surgical procedure was well developed and standardised, ICC was expected to be virtually zero and the proposed sample size was hoped to have closer to 90% power.

The impact of loss to follow-up was minimal for the primary end point (haemorrhoidal recurrence at 12 months). Patients who did not complete their 12-month follow-up still had their hospital notes reviewed, and their GP was contacted to ascertain whether or not any complications or operative procedures were recorded. The only dropout expected was if the patient should die, move out of the area or have no traceable patient notes; we anticipated this would be less than the 5% that we allowed for in this patient population (a previous study of RBL that used only clinical follow-up reported a 1-year loss to follow-up of 10%[51]).

Explanation of any interim analyses and stopping guidelines

No formal interim analyses for efficacy were carried out. However, the safety of the treatments was assessed by an independent DMEC, the members of which convened annually to review SAEs experienced by study participants.

TABLE 1 Use of assessment instruments during the trial

Assessment instrument	Time of assessment						
	Randomisation	Pre-surgery (baseline)	1 day	7 days	21 days	6 weeks	1 year
EQ-5D–5L	○	○	●	●	●	○	●
Visual analogue pain score	○	○	●	●	●	○	
Vaizey incontinence score	○	○					●
Haemorrhoids symptom score	○	○				○	●
Complications review interview						○	●a
Health and social care resource-use data						○	●a
Further treatment questionnaire						○	●a
Recurrence (primary outcome)							●a
Clinical appearance at proctoscopy (when applicable)						○	

a Supplemented by hospital/GP notes.
○, assessment in clinic; ●, telephone/postal self-report assessment.

Randomisation and blinding

Randomisation was undertaken using the CTRU's web-based randomisation system. After consent, participants were individually randomised, in a 1 : 1 ratio, to either HAL or RBL by a member of the research team at site. To ensure equal allocation across centres, randomisation was stratified by centre using permuted blocks of random sizes 2, 4 and 6. Allocation concealment was achieved by ensuring that the participant identifier was entered, following which the allocation was revealed; no member of the study team had access to the randomisation schedule during recruitment. The study was open label, with no blinding of participants, clinicians or research staff attempted.

Statistical methods

Analysis populations

The primary analyses were intention-to-treat (ITT) analyses in which individuals were analysed according to the treatment to which they were randomised, regardless of whether or not they underwent their allocated surgery. Secondary analyses were undertaken on a per protocol (PP) basis, which was restricted to those individuals who complied with the protocol. The categories of non-compliance were eligibility, missed windows, consent and treatment issues, which included patients who did not receive their allocated treatment. Safety summaries were reported, based both on randomised and actual treatment where these differed.

Analysis of 1-year recurrence (primary outcome)

The primary outcome was the recurrence of haemorrhoids at 1 year, as defined above (see *Primary outcome measure*). Analyses were undertaken using a random intercept logistic regression model in which the covariates were treatment allocation, gender, age at surgery and history of previous intervention as fixed effects; the surgeon was included as a random effect. Further sensitivity analyses assessed whether or not other baseline characteristics [including symptom score, EQ-5D-5L and body mass index (BMI)] altered the strength of the treatment effect and/or appeared to modify the treatment effect. 'Goodness of fit' of the logistic regression model was assessed using the Hosmer–Lemeshow test.[52] ICC coefficients were calculated to summarise the clustering that may exist around surgeons.

Secondary outcomes

Persistent significant symptoms at 6 weeks

Recurrence at 6 weeks was analysed in the same manner as the primary outcome. Unlike the 12-month recurrence, no blind review was incorporated, as common symptoms (e.g. severe pain or bleeding) may be due to the procedure rather than the haemorrhoids.

Haemorrhoid symptom severity score

The severity of haemorrhoidal symptoms was compared using a generalised least squares regression mixed model using the same covariates as the primary outcome. The prespecified analysis did not include baseline symptoms as a covariate because of the concerns noted below (see *Important Changes to Methods after Trial Commencement*), but sensitivity analyses were also undertaken, which adjusted for severity at randomisation (when available) and at baseline, and the average of the two. The difference in symptom severity was compared separately for the 6-week and 12-month time points.

European Quality of Life-5 Dimensions (5-level version) status

Health utility was assessed by the EQ-5D-5L questionnaire using the Value Set for England normative data.[53] EQ-5D-5L was assessed at days 1, 7 and 21. Longitudinal analyses of EQ-5D-5L were conducted as part of the economic evaluation described below (see *Health-economic methods*).

Vaizey faecal incontinence score

Incontinence was assessed using the Vaizey inventory and analysed in the same manner as haemorrhoidal symptoms.

Pain

Pain was measured using a 10-cm VAS. The VAS scores for HAL and RBL were compared at each time point using the same methods as the haemorrhoid symptom severity. The VAS was collected at randomisation, baseline, days 1, 7 and 21, and, finally, at 6 weeks.

Safety outcomes

Complications

The secondary outcome of procedural complications (adverse events such as 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 1 year post surgery, was compared between the two groups at each time point using Poisson regression.

Serious adverse events

An adverse event is recorded as 'serious' if it is an untoward occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect, *or*
- is otherwise considered medically significant by the investigator.

Serious adverse events were reported as the number of events, and the number and percentage of participants experiencing each event. Each SAE was classified as systemic complication; urinary retention; pelvic sepsis; or other.

Further treatment

The incidence of the need for further treatment, either surgical or medical, was recorded.

Clinical appearance at proctoscopy (if persistent significant symptoms)

Data were recorded for patients who underwent examination at 6 weeks. This included the clinical assessment of grade and the change from baseline.

Additional/post hoc analyses

Additional, unplanned analyses were undertaken to address questions that arose during the trial progression. These were undertaken in a similar manner to the analyses described above, with adjusted analyses using the same covariates unless otherwise stated.

General considerations

All analyses were undertaken on an ITT basis unless otherwise stated. All confidence intervals (CIs) were two-sided 95% intervals, and all statistical hypotheses were two-sided tests. Continuous measures were summarised as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate to the distribution of the data. Categorical data were summarised as numbers and percentages.

Health-economic methods

Background

We collected data as part of the trial that allowed us to conduct a full economic evaluation. The main economic analysis focused on estimating the incremental cost per QALY of HAL compared with RBL over the 12-month follow-up period of the trial. We have also presented results in terms of the incremental cost per recurrence avoided.

Patients were asked to complete the EQ-5D-5L instrument at pre-randomisation, pre-surgery (baseline) and subsequent time points following the treatment. The UK population tariffs were then used to calculate QALYs for each patient.[54] EQ-5D has been applied in previous studies in this area[55] and appears to be sensitive to changes in patient outcomes. Pain was 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-5L instrument.

Overview

Aim

The aim of the economic evaluation was to assess the cost-effectiveness of HAL compared with RBL in terms of incremental cost per QALYs over 12 months' follow-up.

Methods

Perspective

The economic evaluation took a NHS and Personal Social Services perspective as per NICE recommendations.[49] The estimated resource use covers the period in which a patient is in hospital, post discharge and primary care services, including costs related to recurrence of haemorrhoids.

Method of economic evaluation

We conducted a cost–utility analysis (CUA) as the main method of economic evaluation, for which the outcome was expressed in QALYs. We then carried out a cost-effectiveness analysis (CEA) for which the outcome was expressed in terms of incremental cost per recurrence avoided with HAL compared with RBL. All health-economic analyses were conducted on an ITT basis, including all of the patients randomised to each group. All analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX, USA).

Outcomes

The EQ-5D-5L was used for collecting QoL data at seven time points: pre-randomisation, baseline, 1 day, 7 days, 21 days, 6 weeks and 12 months. The EQ-5D is a generic standardised instrument for measuring HRQoL. The EQ-5D-5L is a five-level version of the EQ-5D, which was recently launched to improve sensitivity of the descriptive system while keeping the same structure of the original instrument [European Quality of Life-5 Dimensions, 3-level version (EQ-5D-3L)].[53] The EQ-5D-5L utility scores we applied were obtained using recently published tariffs based on the UK general public.[54] The individual patient-level QALYs were calculated from EQ-5D-5L scores at baseline and subsequent follow-up time points for 1 year using the area under the curve method. Discounting was not used for the calculated QALYs in the main analyses, as it was carried out for a 1-year time horizon. We examined the relationship between EQ-5D-5L and symptom scores to check the appropriateness of using this instrument in this setting.

Costs

The costing approach followed the standard stages used in economic evaluation and involves identification of resource use, measurement and valuation.[56]

Resource use

Identification of resource use

We identified a range of resource use based on different CRFs and questionnaires used for collecting relevant data at different time points of the trial follow-up. These include the procedure details, clinical assessment at 6 weeks, consultant questionnaire at year, GP questionnaire at 1 year, and participant questionnaire at 1-year time points. The resource use identified is categorised in the following three domains:

Resource use during rubber band ligation procedure

- Procedure event.
- Procedural complications.
- Postprocedural complications.
- Hospital admissions.
- Medication on discharge.

Resource use during haemorrhoidal artery ligation procedure

- Anaesthetic.
- Procedure event.
- Intraoperative complications.
- Hospital admissions.
- Postoperative complications.
- Medication on discharge.

Post discharge

- Outpatient treatments.
- Surgical treatments.
- Emergency admissions.
- Contact with health professionals.
- Further treatments and medications.
- Recurrence treatments.

Measurement of resources

All events relating to resource use identified were recorded throughout the trial using different data collection forms at different time points. These were the procedure details form at day 0, clinical assessment form at 6 weeks, consultant questionnaire at 1 year, and GP questionnaire at 1 year. The instruments used for measuring resource use within the trial are provided in *Appendix 2*. For the HAL procedure event, resource use included the type of anaesthetic used, grade of operating surgeon, whether or not the procedure was supervised by a consultant, timing for surgery, and overall time spent in the operating theatre. Detailed medications prescribed on discharge or as further treatment were also recorded.

Data on hospital admissions and type of admissions were recorded, and data on the durations of admissions were measured based on the NHS average estimates for some events, such as non-elective emergency admissions. Visits for health-care professionals including consultants, GPs and general practice nurses were recorded. However, the duration of each visit was not recorded and therefore average estimates were used based on the NHS or the Personal Social Services Research Unit (PSSRU), University of Kent approaches, where relevant.[57]

Valuation of resources

Costs were estimated in UK pound sterling based on the financial year 2014–15. Unit costs were applied for each resource-use event at the individual patient level to calculate the total cost of resource use over a 12 months' time horizon.

Unit costs

Procedure event unit cost

The unit cost for a RBL procedure event was estimated as an outpatient procedure, and was obtained from the National schedule of NHS reference costs for 2014–15.[58] Admissions unit costs were also obtained from the NHS reference costs.[58] For a HAL procedure, a microcosting approach was applied, based on cost

per minute in procedure, recovery time and theatre overhead per minute. The cost per minute in procedure was based on the actual time spent by clinical staff operating and supervising the procedure and the PSSRU staff unit cost. The unit costs for the surgical kits used in the HAL procedure were obtained from the NHS supply system. Blood transfusion unit cost was obtained from the blood transfusion costing statement issued by NICE.[59] Unit costs for medications prescribed on discharge were calculated using the cost of generic drugs from the *British National Formulary* (BNF) 2015.[60]

Post discharge unit cost

The unit costs for surgical treatments following recurrence of haemorrhoids were obtained from different sources. The cost for SH procedure was taken from McKenzie *et al.*[55] and adjusted for inflation. Unit costs for excisional haemorrhoidectomy (EH) and RBL in the theatre procedures were estimated using the NHS reference costs 2014–15.[58] The unit costs for repeated RBL and HAL procedures were calculated using the average cost for participants within the HubBLe trial. For contacts with health-care professionals, the PSSRU unit costs were applied.

All unit costs used in the economic analyses are summarised in *Tables 2–4*.

Outcomes

Recurrence is the primary outcome for this study (please refer to *Primary Outcome Measure*, above, for details). For the economic evaluation, the difference in the number of recurrence between the intervention group (HAL) and the control group (RBL) was used as an outcome for assessing the cost-effectiveness in terms of cost per recurrence avoided.

Analysis

The base-case analysis was based on imputed data, whereas complete-case analysis was conducted as a sensitivity analysis. The economic analysis involves CUA as a primary analysis, and a CEA was performed as a secondary analysis. Both analyses involve the estimation of differential costs and differential outcomes.

A subgroup analysis was performed for patients with new haemorrhoids and patients with recurrence following RBL before randomisation. Different sensitivity analyses were performed to address uncertainty associated with the estimates from our base-case analysis.

TABLE 2 Unit cost applied for valuation of resource use: RBL procedure

Event	Description	Unit cost (£)	Source	Note
Procedure cost	RBL procedure	109.00	*UK NHS reference costs 2014–15*[58]	Outpatient procedure
	Blood transfusion	170.14	NICE 2015[59]	Blood transfusion costing statement
Hospital admission	Inpatient bed-day	303.00	*UK NHS reference costs 2014–15*[58]	–
Medication prescribed post procedure	Paracetamol	1.27	BNF 2015[60]	500 mg, 32-tablet pack
	Co-codamol	6.73	BNF 2015[60]	30/500 mg, 100-tablet pack
	Codeine	1.23	BNF 2015[60]	15 mg, 28-tablet pack
	NSAID	3.50	BNF 2015[60]	Ibuprofen 200 mg, 84-tablet pack
	Tramadol	14.10	BNF 2015[60]	100 mg, 30-tablet pack
	Laxative	3.82	BNF 2015[60]	Bisacodyl 5 mg, 100-tablet pack
	Antibiotic	5.03	BNF 2015[60]	Augmentin[a] 375 mg, 21-tablet pack

NSAID, non-steroidal anti-inflammatory drug.
a Augmentin = amoxicillin and clavulanate potassium.

TABLE 3 Unit cost applied for valuation of resource use: HAL procedure

Event	Description	Unit cost (£)	Source	Note
Anaesthetic	General and local anaesthetic	100.08	*UK NHS reference costs 2014–15*[58]	
	Spinal anaesthetic	200.00		
HAL procedure	Consultant cost per minute	2.30	PSSRU 2015[57]	Includes costs of qualifications
	Associate specialist cost per minute	2.13	PSSRU 2015[57]	Includes costs of qualifications
	Surgical trainee cost per minute	2.13	PSSRU 2015[57]	Includes costs of qualifications
	Fellow cost per minute	2.13	PSSRU 2015[57]	Includes costs of qualifications
	Specialist nurse cost per minute	1.52	PSSRU 2015[57]	Includes costs of qualifications
	Research nurse cost per minute	1.52	PSSRU 2015[57]	Includes costs of qualifications
	Registrar cost per minute	1.20	PSSRU 2015[57]	Includes costs of qualifications
	Scrub nurse cost per minute	1.52	PSSRU 2015[57]	Includes costs of qualifications
	Cost per minute in recovery	0.41	McKenzie 2009[55]	Adjusted for inflation
	Cost per minute for theatre overheads	13.74	McKenzie 2009[55]	Adjusted for inflation
Operating event	Outpatient procedure	109.00	PSSRU 2015[57]	
	Surgical kit for HAL procedure	432.00	NHS Supply system	
	Excision of skin tags	109.00	*UK NHS reference costs 2014–15*[58]	Outpatient procedure
Procedure cost	Cost of HAL surgery (used in sensitivity analysis)	1128.00	*UK NHS reference costs 2014–15*[58]	Intermediate anal procedure (FZ22B-E)
Hospital admission	Inpatient bed-day	303.00	*UK NHS reference costs 2014–15*[58]	
	Need for blood transfusion	170.14	NICE 2015[59]	Blood transfusion costing statement
Medication on discharge	Paracetamol	1.27	BNF 2015[60]	500 mg, 32-tablet pack
	Co-codamol	6.73	BNF 2015[60]	30/500 mg, 100-tablet pack
	Codeine	1.23	BNF 2015[60]	15 mg, 28-tablet pack
	NSAID	3.50	BNF 2015[60]	Ibuprofen 200 mg, 84-tablet pack
	Tramadol	14.10	BNF 2015[60]	100 mg, 30-tablet pack
	Laxative	3.82	BNF 2015[60]	Bisacodyl 5 mg, 100-tablet pack
	Antibiotic	5.03	BNF 2015[60]	Augmentin 375 mg, 21-tablet pack
	GTN paste	39.30	BNF 2015[60]	GTN ointment 0.4%, 30 g
	Diltiazem paste	73.83	BNF 2015[60]	2% diltiazem cream

GTN, glyceryl trinitrate; NSAID, non-steroidal anti-inflammatory drug.

TABLE 4 Unit cost applied for valuation of resource use: post discharge (RBL or HAL)

Event	Description	Unit cost (£)	Source	Note
Outpatient treatment	Outpatient visit	114.00	*UK NHS reference costs 2014–15*[58]	
	Injection sclerotherapy	4.79	BNF 2015[60]	Phenol 5% injection, 5-ml ampoule
	EH	1508.72	*UK NHS reference costs 2014–15*[58]	FZ22E (elective)
	SH	2478.42	McKenzie 2009[55]	Adjusted for inflation
	RBL (in theatre)	1338.45	*UK NHS reference costs 2014–15*[58]	FZ22E (elective)
	Other elective procedure	1338.45	*UK NHS reference costs 2014–15*[58]	FZ23A
Emergency admissions	Emergency admission for symptoms related to RBL/HAL	1565.00	*UK NHS reference costs 2014–15*[58]	Non-elective
	Blood transfusion	170.14	NICE 2015[59]	Blood transfusion costing statement
	Emergency operation	2761.00	*UK NHS reference costs 2014–15*[58]	FZ23A
Contact with health professionals	GP visit	46.00	PSSRU 2015[57]	
	Nurse visit (GP practice)	13.70	PSSRU 2015[57]	Based on 15.5 minutes per visit
	Consultant visit	114.00	*UK NHS reference costs 2014–15*[58]	
Further treatments	GTN paste	39.30	BNF 2015[60]	GTN ointment 0.4%, 30 g
	Diltiazem paste	73.83	BNF 2015[60]	2% Diltiazem cream
Recurrence treatment costs	Proctoscopy at 6 weeks' assessments	10.99		
	RBL after recurrence	523.16	Mean RBL cost within HubBLe trial	
	Admissions with complications	1565.00	*UK NHS reference costs 2014–15*[58]	Non-elective

GTN, glyceryl trinitrate.

Resource use

Resource-use data were used for costing the different clinical events and service use at individual patient level. Where RBL or HAL procedures are repeated following recurrence after the initial procedure within this trial, the mean level of resource use within the HubBLe trial was applied.

Difference in costs

The mean total costs and the differences in mean total costs between HAL and RBL groups were analysed using complete-case analysis and descriptively reported alongside the numbers of complete cases, their percentage from the total participants per group, SDs and CIs. The mean costs for each group of resource-use items were similarly reported in tabular format.

Missing data

Missing data may lead to misleading estimates of within-trial CEA, and in this context complete-case analysis is undesirable, as it would reduce the sample size and may affect the power of the study.[61]

To check the patterns of missing data, we performed two types of descriptive analyses of missing data: (1) number of missing data by treatment group to assess whether or not missing data differ by group; and (2) missing data patterns to determine whether or not data are missing for all items or individual items of utility scores and resource-use items over the trial follow-up.[61] The multiple imputation chained equation (MICE) method with predictive mean matching was utilised for imputing missing values of costs, QALYs and baseline utility.[61] Age, gender, grade of haemorrhoids, site code and randomisation group were used as imputation variables in this model. The number of imputations specified in this model was 53, based on the highest percentage of missing data for the variables of interest (baseline utility, QALYs and total cost).[61] The imputation was performed per randomisation arm, for all imputed variables, except baseline utility, for which imputation was performed across all observations. This model allowed the prediction of missing values from the posterior distribution of missing observations, given the values of observed data from the imputation variables.

Cost–utility analysis

Cost–utility analysis was performed as the primary economic analysis for estimating the cost-effectiveness of HAL compared with RBL. A seemingly unrelated regression (SUR) model was fitted for estimating differential costs and differential QALYs, while controlling for imbalance in baseline utility and taking into account the correlation between cost and QALYs. Controlling for imbalance in baseline utility is recommended as good practice for within-trial CEA.[62] The fitted SUR model also provided the estimation of full variance–covariance matrix which was further used for addressing uncertainty using the parametric method.[63] In addition to the advantage of controlling for heterogeneity between patients (such as an imbalance in baseline utility) offered by traditional ordinary least squares (OLS) regression, SUR offers two additional advantages: it allows (1) the use of different sets of covariates for cost and effectiveness (QALYs) to assess their joint impact on cost-effectiveness simultaneously; and (2) the testing of joint hypothesis regarding the important coefficients (difference in costs and QALYs) across the two regression equations.[63]

The incremental cost-effectiveness ratio (ICER) was estimated from the SUR regression output, based on analysis of imputed data for the base case. The ICER is then compared with NICE cost-effectiveness threshold range of £20,000–30,000 per QALY gained.

To address uncertainty around our CUA estimates, a number of approaches were used based on the parametric method. We used five key parameters from the SUR regression output and conducted a fully parametric CUA. These parameters were difference in mean QALYs, standard error (SE) of the mean differential QALYs, difference in mean costs, SE of mean differential costs, and covariance between costs and QALYs. From these parameters, we produced three different graphs: the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness confidence ellipses and the net benefit line with CIs. The higher bound of NICE cost-effectiveness threshold of £30,000 per QALY was used as a standard decision rule in this analysis for illustrative purposes. The cost-effectiveness threshold was varied from £0 to £140,000 for addressing uncertainty associated with the cost–utility estimates across different levels of willingness to pay.

Combined CEAC curves were generated from the subgroup analysis for patients with new haemorrhoids and patients with recurrence following RBL to allow for easy comparisons. We also conducted an additional analysis by controlling for the grade of haemorrhoids in addition to baseline utility within the SUR model. This allowed us to assess the effect of the grade of haemorrhoids on our CUA in terms of differential cost, differential QALYs and the ICER.

Cost-effectiveness analysis

The CEA followed the standard approach for which the total difference in costs was divided by the difference in recurrence to generate the incremental cost per recurrence avoided. However, it should be noted that treatments differed following recurrence, and these were also captured by our costing approach and constitute a key part within the primary CUA.

Sensitivity analyses

We performed a number of sensitivity analyses to assess the robustness of our estimates and address some issues, which might be associated with our costing approach and unit costs applied in the base-case analysis. The main sensitivity analysis was based on using the NHS reference costs for HAL procedure rather than the microcosting approach. In this scenario, HAL was considered as a day case intermediate anal procedure and the cost associated with this Healthcare Resource Group (HRG) was applied. This was assumed to include all of the other procedure-related costs, including the anaesthetic cost, the surgical kits, staff time and theatre overhead cost as per the HRG costing approach. A similar imputation model and SUR were used for estimating differential cost, differential QALYs and the ICER for this scenario of sensitivity analysis. We also produced a CEAC curve using the same methods applied in our base-case analysis.

An additional sensitivity analysis was undertaken by controlling for the grade of haemorrhoids, in addition to baseline utility, using the same regression model. This was carried out to assess the interaction effect of the grade of haemorrhoids on our CUA. The results from this form of sensitivity analysis are presented in terms of ICER.

We also carried out a sensitivity analysis by conducting another scenario of CUA using complete cases. A similar SUR model was run for estimating differential costs, differential QALYs and the ICER based on complete cases only. The results of this analysis were reported in a tabular format.

Another sensitivity analysis was conducted by estimating a utility decrement for each subsequent procedure performed during the trial follow-up. As the EQ-5D-5L questionnaire was completed at particular follow-up time points that did not coincide with any follow-up procedures, estimated QALY decrements were applied. The QALY decrements following subsequent HAL or RBL procedures were estimated using mean utility scores from the trial at baseline, day 1 and day 7. For SH and EH utility decrements were taken from a published UK study.[2] Utility scores during the recovery period of 0.756 for EH and 0.767 for SH were used for estimating QALY decrements.[2] QALY decrements were applied at the individual patient-level data and a regression analysis was run using the same model specification in our base-case analysis.

Long-term cost-effectiveness

A long-term extrapolation analysis was undertaken to assess the cost-effectiveness of HAL compared with RBL beyond the trial time horizon. The cost and utility data reported at 1-year follow-up within the trial were used in combination with external data to estimate longer-term costs and QALYs. A time horizon of 3 years beyond the trial was chosen for this analysis. This choice of time horizon was driven by data from external studies for which recurrence data were available over this follow-up time. We constructed a three-health states Markov model for extrapolating within-trial cost–utility analyses to long-term cost-effectiveness. To maintain consistency with the trial analyses, health states were chosen based on the primary outcome of the trial – recurrence. Heath states included were new haemorrhoids, recurrence and no recurrence. The extrapolation model structure is shown in *Figure 2*.
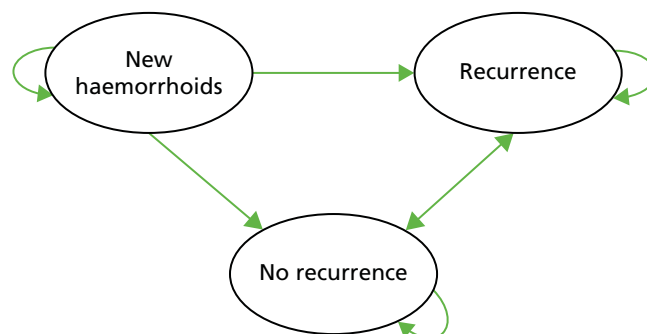
FIGURE 2 Extrapolation model structure.

Regression analysis was used to estimate costs and utilities from the trial data using a similar SUR model described earlier, with recurrence at baseline added as a covariate. This allowed us to estimate costs and utilities by health state. We assumed that costs and outcomes follow the same pattern observed within the trial for the purpose of these extrapolation analyses. For instance, the mean costs and QALYs for patients with recurrence following RBL after 1 year and treated with further procedures were assumed to be same. Costs and health benefits (utilities) occur at different time points within the long-term time horizon of this analysis. We used the UK Treasury discount rate of 3.5% per year for discounting all future costs and QALYs as recommended by NICE.[49]

The annual probability of recurrence for years 1–3 beyond the trial were estimated from two studies[3,37] that have reported long-term recurrence estimates. For RBL, the annual probability of recurrence was calculated from a retrospective study[3] that reported 4 years' follow-up ($n = 805$). For HAL, the probability of recurrence was calculated at 5-year follow-up in a study[37] that assessed the long-term success rates for treating patients with grade II and III haemorrhoids following Doppler-guided HAL ($n = 100$).[37] The mean total costs over four years, per patient, within each group (HAL and RBL) were calculated based on the annual probabilities of transition between health states. The mean total QALYs over the same period were similarly estimated and adjusted for recurrence. The long-term ICER was then estimated from the model and is reported below (see *Long-term cost-effectiveness*).

A probabilistic sensitivity analysis (PSA) was performed to address the uncertainty around parameter estimates from external sources (i.e. long-term recurrence rates). The PSA was run on 1000 Monte Carlo simulations. The distribution of costs and QALYs used in the PSA simulations were estimated from the regression analysis on the trial data.

Patient and public involvement

We were committed to involving service users at each stage of our research, from design to dissemination. From our patient and public consultation event, we identified an individual who was willing to join the grant application team. This person attended the TSC meetings in order to provide input into study oversight and have commented on the report, particularly the plain language summary, and the patient view regarding the choice of treatment. We also had input from service users with regards to the study design, including some of the patient questionnaires and the length of follow-up involved, and sought the TSC member's opinion on study documents submitted to the REC, both initially and relating to protocol amendments.

Chapter 3 Results

Recruitment and participant flow

Participants who were randomly assigned, received intended treatment and were analysed for the primary outcome

Recruitment to the trial is represented in *Figure 3*. A total of 372 participants were randomly assigned to receive RBL or HAL; 187 patients were allocated to receive RBL, and 185 were allocated to receive HAL. Two of these participants (both randomised to RBL) were removed from the trial completely, as they were ineligible at the time of consent; therefore, a total of 370 participants were entered into the trial. In total, 969 patients were screened for entry into the trial and the reasons for non-recruitment are shown in *Table 5*.

Patient preference was the main reason for non-consent by patients, with 128 patients opting for RBL and 70 patients opting for HAL.

Losses and exclusions after randomisation

A total of 340 participants received treatment as part of the trial and the participant flow is shown in *Figure 4*; reasons for withdrawal during the trial are provided in *Table 6*. Primary outcome data were collected for 337 participants (161 HAL and 176 RBL): 256 patient questionnaires were returned at 12 months; 236 GP forms were returned at 12 months, and 337 consultant forms were completed at 12 months. There were 183 participants where all 3 of the 12 months forms were completed/returned.

Dates defining the periods of recruitment and follow-up

The first site to open to recruitment was STH NHS Foundation Trust on 9 September 2012, and recruitment finished at all sites on 6 May 2014. Follow-up was due to end 1 year after the end of recruitment but to allow for the delay in receiving the trial treatment we extended this period and the follow-up was completed at sites on 28 August 2015.

Table 7 shows the duration between randomisation and treatment (waiting time) by treatment group for the trial. These data do not include individuals who withdrew prior to treatment; 24 participants withdrew prior to the procedure in the HAL group, compared with six (eligible) participants in the RBL group. In the RBL group, 114 of 179 (63.4%) participants received treatment on the same day as they were randomised (0 days), whereas none of the HAL group participants was treated on the same day. Although the maximum waiting time is greater for RBL, the mean and median shows that waiting times are higher for HAL.

Baseline data

The characteristics of the participants included in the final analysis is shown in *Table 8*. The groups appear balanced at baseline in regards to gender, age, BMI, the grade of haemorrhoids and previous treatment for haemorrhoids.

The majority of the procedures were conducted by consultant or equivalent (clinician accredited for independent practice, including a clinical nurse specialist), or supervised by a consultant (87% for RBL and 96% for HAL). There were a few cases that were carried out by a trainee doctor. However, these trainees met our pre-existing competencies.
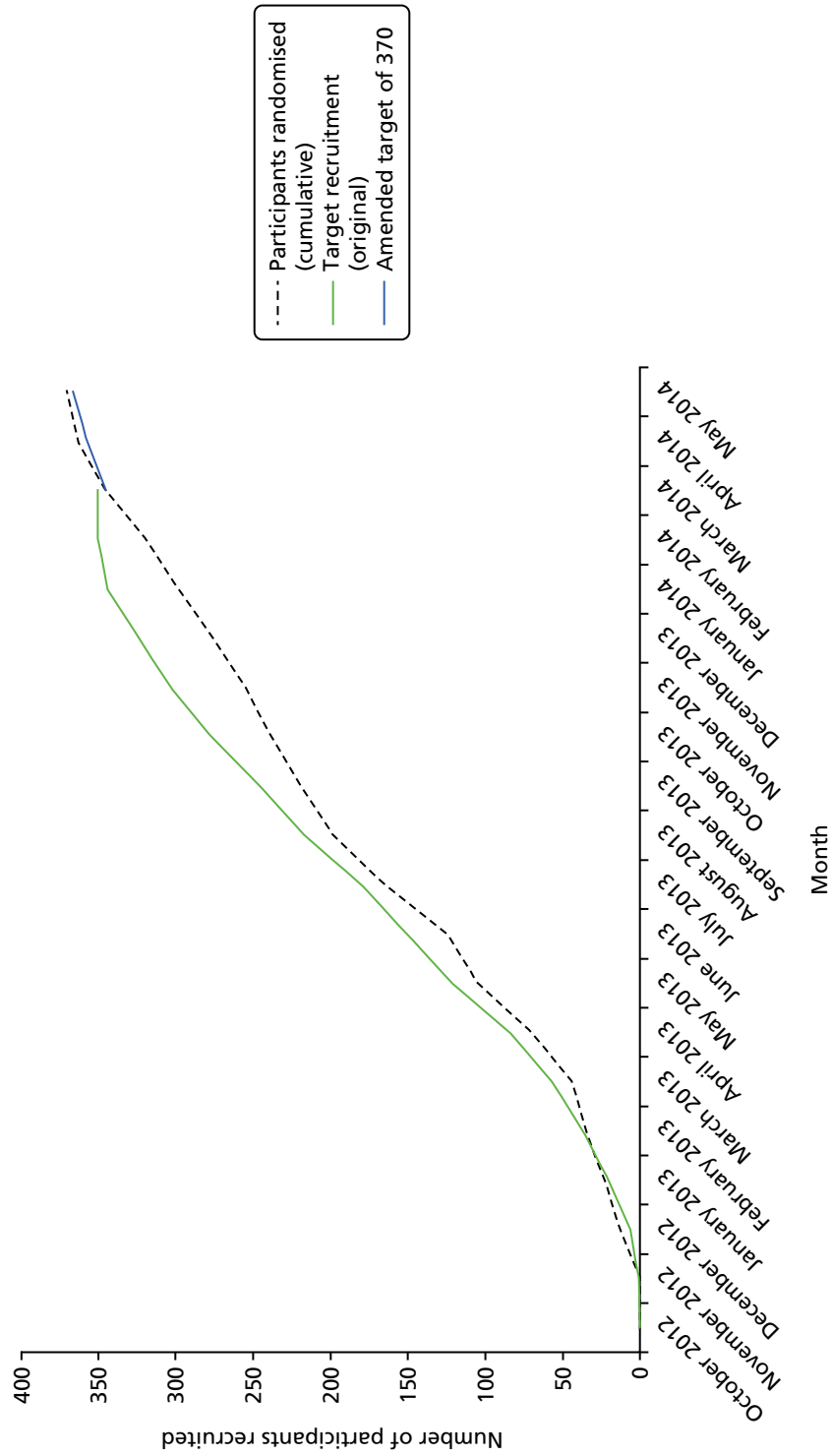
FIGURE 3 Recruitment graph.
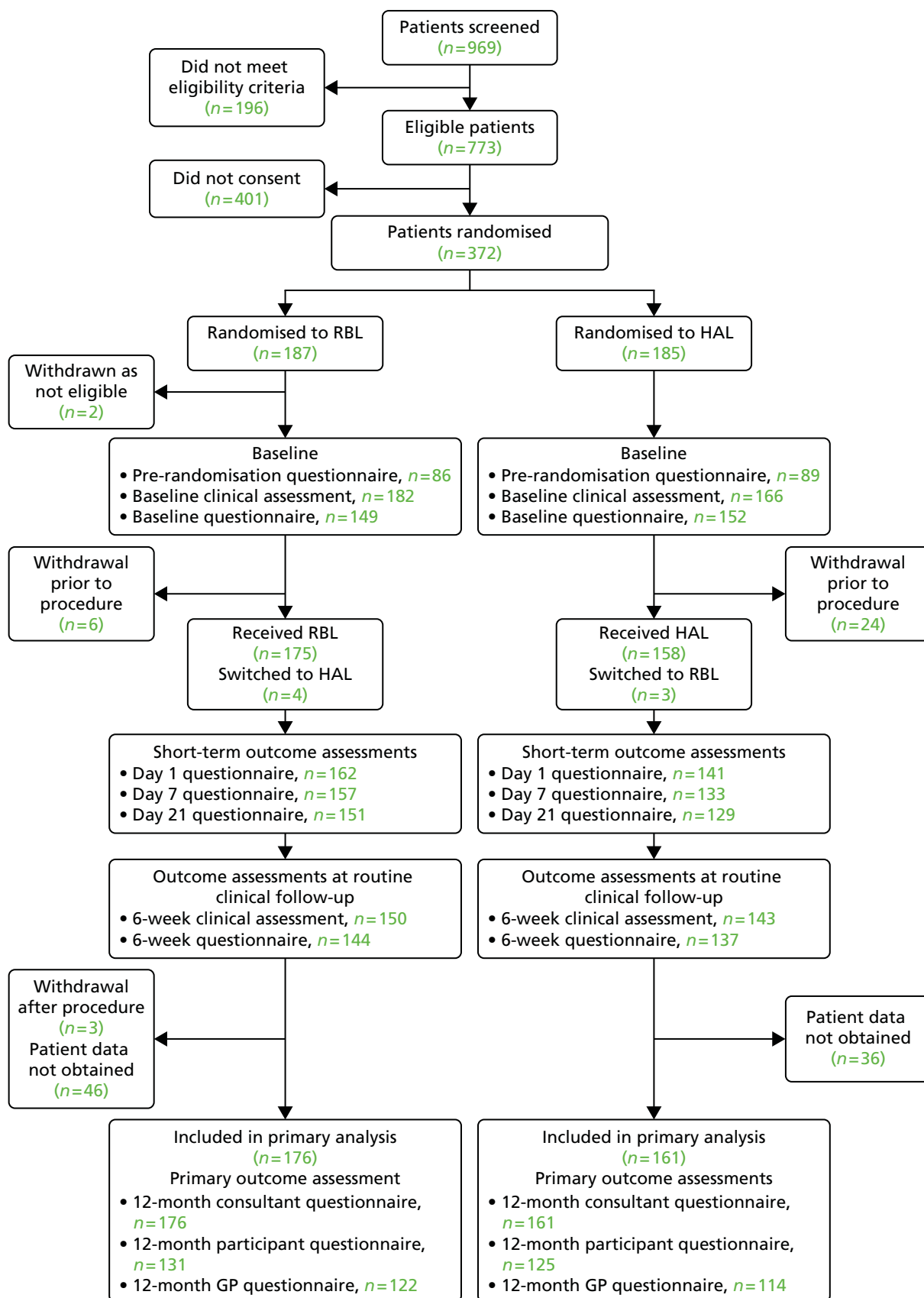
FIGURE 4 Flow chart summarising the numbers of each type of questionnaire completed throughout the trial.

TABLE 5 Reasons for non-recruitment to the trial for eligible patients

Reason	Frequency
Patient preference	251
Patient preference for RBL	128
Patient preference for HAL	70
Patient preference for other surgery	5
Patient preference for immediate treatment	3
Patient preference related to general anaesthetic	6
Patient did not want any intervention or treatment	39
Clinical decision	41
Patient did not attend appointment/uncontactable	26
Patient unsure or declined (no further reason given)	29
Other reason	12
Unknown	42
Total	401

TABLE 6 Reasons for participant withdrawal during the trial

	Treatment group	
Reason for withdrawal	HAL (*n* = 24)	RBL (*n* = 11)
Prior to procedure		
Found to be ineligible during baseline assessments	0	2
Participant withdrew consent	15	3
Lost to follow-up prior to procedure	6	2
Symptoms resolved	2	1
Ineligible at time of procedure	1	0
After procedure		
Participant withdrew consent	0	3

TABLE 7 Duration between randomisation and treatment in the trial (waiting time)

	Waiting time (days)			
Treatment group	Minimum	Maximum	Mean	Median
HAL	2	276	75.9	62
RBL	0	413	20.3	0

TABLE 8 Baseline demographical data by randomised group

Demographic	Value	Treatment group	
		RBL (*n* = 176)	HAL (*n* = 161)
Gender	Male (%)	99 (56)	85 (53)
	Female (%)	77 (44)	76 (47)
Age	Mean (SD)	49.0 (12.9)	48.5 (13.5)
	Median (IQR)	50.5 (38.5–58.0)	49.0 (38.0–60.0)
	Range	21.9–79.3	20.2–74.6
BMI	Mean (SD)	28.0 (5.5)	28.2 (7.1)
	Median (IQR)	27.0 (24.4–31.7)	26.8 (24.1–30.0)
	Range	17.4–44.9	18.8–67.4
Grade	II (%)	115 (65)	92 (57)
	III (%)	60 (34)	68 (42)
	Not recorded (%)	1 (0.6)	1 (0.6)
Previous treatment	No (%)	124 (70)	124 (77)
	Yes (%)	52 (30)	36 (22)
	Not recorded	0	1 (0.6)
Grade of surgeon undertaking procedure	Consultant or equivalent (%)	148 (84)	121 (75)
	Junior trainee, supervised by consultant (%)	6 (3)	34 (21)
	Junior trainee, not supervised by consultant (%)	22 (13)	6 (4)

Numbers analysed

The ITT population, in which patients were analysed by their original assigned groups, included all 161 participants in the HAL arm and 176 in the RBL arm for whom recurrence data were available from either the patient, clinician or GP. Of these, the patient-completed questionnaire was returned for 125 and 131 participants in the HAL and RBL groups, respectively. The number of participants included in each analysis is provided for each measure in this section.

Outcomes and estimation

Recurrence (primary outcome)
The overall proportion of participants with a recurrence at 12 months was 49% in the RBL arm compared with 30% in the HAL arm (absolute difference 19.6%; adjusted OR 2.23, 95% CI 1.42 to 3.51; $p = 0.0005$). The breakdown of recurrences, overall and by criterion, is presented in *Table 9*. Self-reported recurrence rates were almost identical, with 29% of respondents in both arms stating that they believed that their haemorrhoids had either improved or been cured (adjusted OR for self-reported recurrence = 1.06, 95% CI 0.60 to 1.85; $p = 0.85$). The increased recurrence associated with RBL is mainly attributable to the high rate of additional procedures undertaken following the initial procedure [33%, compared with 14% in the HAL group (adjusted OR for further procedure = 2.86, 95% CI 1.65 to 4.93; $p < 0.001$)]. A further three (2%) participants in the RBL arm were considered to have symptoms that were consistent with recurrent haemorrhoids following blind review. In two cases the participants were recorded as possibly requiring further treatment at their 6-week visit but were subsequently lost to follow-up; a third patient had been hospitalised twice for excessive bleeding, but had not undergone treatment.

TABLE 9 Recurrence at 1 year

Recurrence	Treatment group	
	RBL (*n* = 176)	HAL (*n* = 161)
Overall recurrence (%)	87 (49)	48 (30)
Criteria for recurrence[a] (%)		
Self-reported recurrence (%)	37 (29[b])	34 (29[b])
Subsequent procedure for haemorrhoids (%)	57 (33)	23 (14)
RBL	31 (18)	14 (9)
HAL	23 (13)	7 (4)
EH	4 (2)	7 (4)
SH	2 (1)	1 (1)
From blinded review (%)	3 (2)	0

a More than one may apply.
b Denominator is patients returning questionnaire.

Sensitivity analyses were undertaken in which alternative covariates (EQ-5D-5L at randomisation or preoperative, BMI at randomisation, and grade of haemorrhoids at randomisation) were adjusted for; doing so yielded reasonable consistency in the ORs (range 2.05–2.81), all of which remained statistically significant. The PP analysis again provided a similar OR (2.21, 95% CI 1.38 to 3.54; $p = 0.001$).

Of the baseline covariates assessed, none had a statistically significant association with recurrence. Recurrences were more common, however, among participants who were male, had grade III haemorrhoids, had undergone previous treatment and had higher symptom scores.

Among the 80 participants who required a further intervention, the majority of participants underwent a single procedure. In most cases this was RBL, as described in *Table 9*, although some variation was noted across centres as described in *Table 10*: as the primary interest is to document second-line treatment, the treatment groups here refer to treatment, as received, as opposed to 'as randomised', which was reported previously. As RBL is a brief procedure with (relatively) minimal inconvenience to the patient, it could be argued that a second-line RBL is not itself indicative of a recurrence because the initial haemorrhoids remain incompletely treated. Consequently, an additional (and unplanned) analysis investigated the extent to which recurrence differed if follow-up RBL were not considered a recurrence. In total, 45 participants (31 in the RBL arm, 11 in HAL) underwent RBL as follow-up procedure. Of the 31 patients who underwent

TABLE 10 Type of second procedure by treating centre

Site	Treatment group							
	RBL (*N* = 175)				HAL (*N* = 162)			
	n	RBL	HAL	Haemorrhoidectomy	*n*	RBL	HAL	Haemorrhoidectomy
Sheffield	39	8	12	0	34	3	0	0
Birmingham	34	8	0	2	31	5	2	2
Oxford	28	4	2	1	29	2	4	3
Liverpool	21	3	2	0	23	2	2	0
North Tees	13	2	0	1	10	1	0	0
Other centres	40	6	6	2	35	1	0	3

Centres included have at least 10 participants per arm; the remainder are classified as 'other'.

repeat RBL, six considered their haemorrhoids to be unchanged or worse at 1 year; three underwent further procedures; and one was considered a recurrence based on blind review. In the HAL arm, 8 of the 11 participants who were undergoing subsequent RBL considered their haemorrhoids to be unchanged or worse at 1 year and two participants underwent further procedures. Thus, if subsequent RBL were not considered a recurrence, the number with recurrent haemorrhoids is 66 (37.5%) in the RBL arm and 44 (27.3%) in the HAL arm (adjusted OR 1.53, 95% CI 0.96 to 2.44; $p = 0.071$). If a single HAL is compared with multiple RBLs the number with recurrent haemorrhoids is 66 (37.5%) in the RBL arm and 48 (30%) in the HAL arm (adjusted OR 1.35, 95% CI 0.85–2.15; $p = 0.20$).

Persistent significant symptoms at 6 weeks

At 6 weeks, data were available for 150 participants in the RBL arm and 143 in the HAL arm: 43 (24%) participants in the RBL arm reported their haemorrhoids as being unchanged or worse compared with 12 (7%) in the HAL arm; additionally, one participant in each arm had subsequently undergone RBL, thus resulting in the overall number of patients with persistent symptoms being 44 (29%) compared with 13 (9%) (adjusted OR 4.35, 95% CI 2.19 to 8.65; $p < 0.001$).

Haemorrhoid symptom severity score

The haemorrhoid symptom severity scores are summarised in *Table 11* and displayed graphically in *Figure 5*: higher scores indicate more severe symptoms. At 6 weeks, haemorrhoids symptom severity scores were higher in the RBL group, indicating that short-term symptoms were less pronounced following HAL. The mean (SD) scores were 4.0 (3.5) in the RBL group and 3.0 (3.1) in the HAL group, with an adjusted mean difference of 1.0 (95% CI 0.3 to 1.8; $p = 0.010$). No difference was apparent at 1 year, with the mean (SD) being 3.6 (3.2) for RBL and 3.6 (3.3) for HAL (adjusted difference = 0.0, 95% CI –0.8 to 0.8; $p = 0.98$).

A further (post hoc) analysis looked at the proportion of participants whose symptom score was either '0' or '1', as this corresponds to the definition used by Nyström *et al.*[42] These numbers are shown in *Table 12*. The proportions are consistent with the previous analysis, with a greater proportion of participants in the HAL arm reporting either a score of 0 or 1 at 6 weeks.
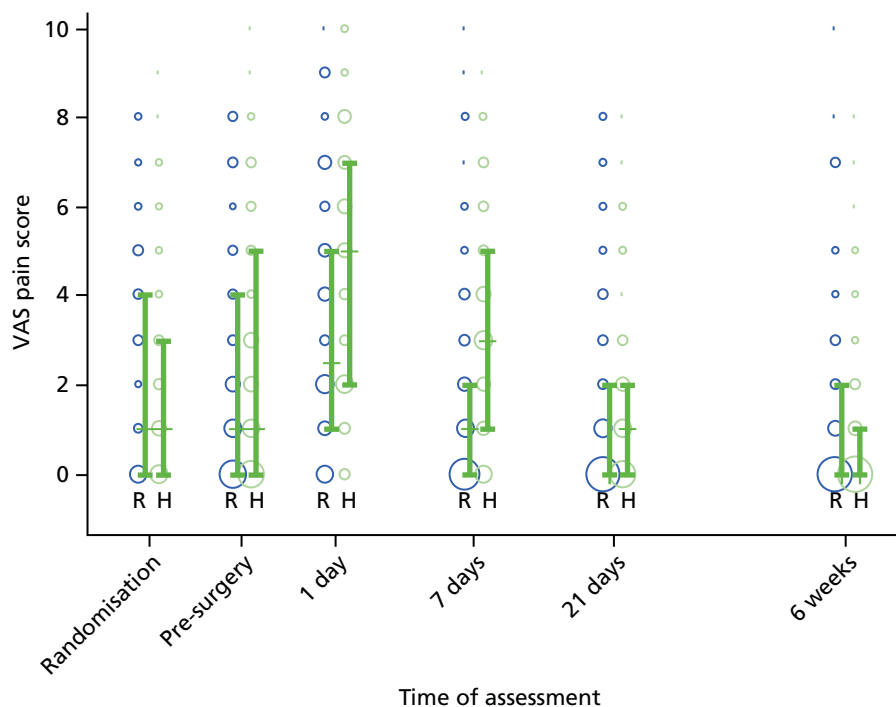
FIGURE 5 Haemorrhoid symptom severity scores. Note that the area of data points is proportional to the number of participants with that value. Vertical lines represent median and IQR.

TABLE 11 Participants with haemorrhoid symptom severity scores

| Time point | Treatment group | | Difference (95% CI); *p*-value |
	RBL	HAL	
Randomisation			
n	83	80	
Mean (SD)	6.5 (3.2)	6.4 (3.4)	
Median (IQR)	6.0 (4.0–8.5)	6.0 (4.0–9.0)	
Baseline			
n	146	150	
Mean (SD)	6.5 (3.3)	6.4 (3.0)	
Median (IQR)	6.0 (4.0–8.0)	6.0 (4.0–8.5)	
6 weeks			
n	142	137	1.0 (0.3 to 1.8); 0.01
Mean (SD)	4.0 (3.5)	3.0 (3.1)	
Median (IQR)	3.0 (1.0–6.0)	2.0 (1.0–5.0)	
12 months			
n	131	123	0.0 (–0.8 to 0.8); 0.98
Mean (SD)	3.6 (3.2)	3.6 (3.3)	
Median (IQR)	3.0 (1.0–5.0)	3.0 (1.0–5.2)	

Mean difference is adjusted for age, gender, prior treatment and surgeon.

TABLE 12 Percentage of participants with haemorrhoid symptom severity scores of '0' or '1'

| Time point | Treatment group | | OR (95% CI); *p*-value |
	RBL	HAL	
Randomisation	2/83 (2%)	4/80 (5%)	
Baseline	2/146 (1%)	5/150 (3%)	
6 weeks	44/142 (31%)	52/137 (38%)	0.73 (0.44 to 1.22); 0.23
1 year	35/131 (27%)	38/123 (31%)	0.79 (0.46 to 1.38); 0.42

Mean difference is adjusted for age, gender, prior treatment and surgeon.

European Quality of Life-5 Dimensions (5-level version)

The EQ-5D-5L health tariff is summarised in *Table 13* and *Figure 6*: higher figures indicate a better health state. Prior to procedure, the mean health utility was around 0.9 in both groups but declined at days 1 and 7 in the HAL group. For RBL the mean (SD) at 1 day was 0.84 (0.19) and at 7 days 0.92 (0.15); in other words, health state was reduced for the first day but had reverted back at 1 week. By contrast, the mean health state for HAL had not returned to baseline values by 7 days, with the mean (SD) being 0.76 (0.22) and 0.83 (0.18) at 1 and 7 days, respectively. The adjusted mean differences were 0.08 (95% CI 0.04 to 0.13; $p < 0.001$) at 1 day and 0.08 (95% CI 0.05 to 0.12; $p < 0.001$) at 7 days. The two arms were nearly similar with no statistical differences (and above baseline values) at all time points from day 21 onwards.

The EQ-5D-5L inventory was also used to derive the health state used in QALYs that are reported within the health-economic analysis in the following section.
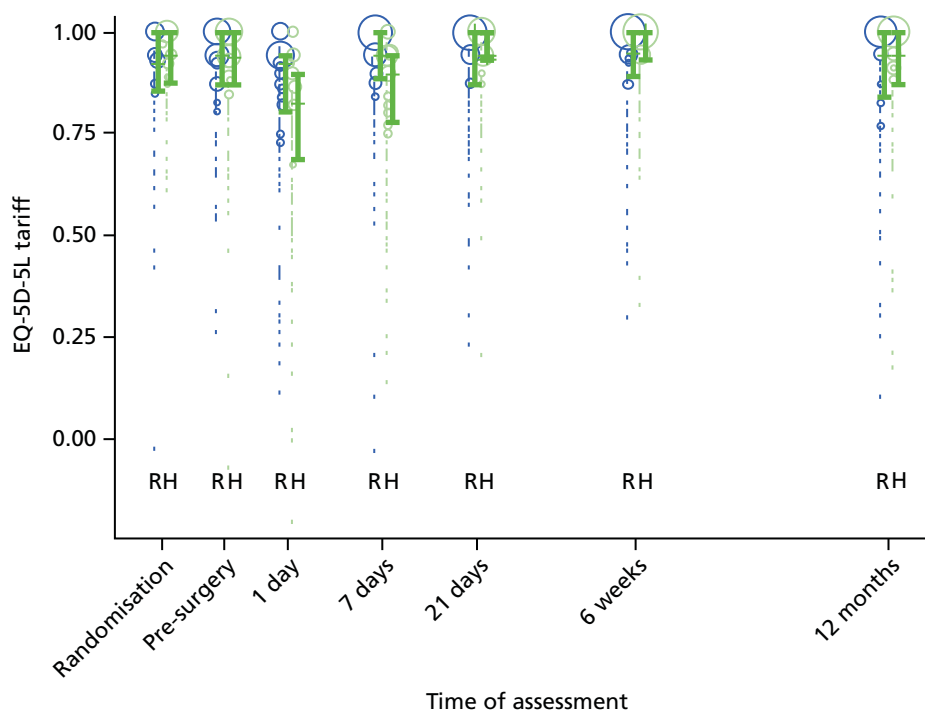
FIGURE 6 The EQ-5D-5L. Note that the area of data points is proportional to the number of participants with that value. Vertical lines represent median and IQR.

TABLE 13 The EQ-5D-5L health utility

Time point	Treatment group		Difference (95% CI); *p*-value
	RBL	HAL	
Randomisation			
n	86	89	
Mean (SD)	0.89 (0.16)	0.92 (0.09)	
Median (IQR)	0.92 (0.86–1.00)	0.94 (0.88–1.00)	
Baseline			
n	149	152	
Mean (SD)	0.90 (0.12)	0.89 (0.15)	
Median (IQR)	0.94 (0.87–1.00)	0.94 (0.87–1.00)	
1 day			
n	162	141	0.08 (0.04 to 0.13); < 0.001
Mean (SD)	0.84 (0.19)	0.76 (0.22)	
Median (IQR)	0.94 (0.87–0.94)	0.82 (0.69–0.90)	
7 days			
n	157	133	0.08 (0.05 to 0.12); < 0.001
Mean (SD)	0.92 (0.15)	0.83 (0.18)	
Median (IQR)	0.94 (0.89–1.00)	0.90 (0.78–0.94)	
21 days			
n	151	129	−0.01 (−0.04 to 0.02): 0.35
Mean (SD)	0.92 (0.14)	0.93 (0.11)	
Median (IQR)	1.00 (0.87–1.00)	0.94 (0.93–1.00)	

TABLE 13 The EQ-5D-5L health utility (*continued*)

| Time point | Treatment group | | Difference (95% CI); *p*-value |
	RBL	HAL	
6 weeks			
n	144	137	−0.02 (−0.05 to 0.01): 0.12
Mean (SD)	0.92 (0.13)	0.94 (0.11)	
Median (IQR)	0.95 (0.89 to 1.00)	1.00 (0.93 to 1.00)	
1 year			
N	128	123	−0.02 (−0.06 to 0.03): 0.46
Mean (SD)	0.89 (0.17)	0.91 (0.16)	
Median (IQR)	0.94 (0.84 to 1.00)	0.94 (0.87 to 1.00)	

Mean difference is adjusted for age, gender, prior treatment and surgeon.

Vaizey faecal incontinence score

Vaizey faecal incontinence scores are provided in *Table 14* and *Figure 7*; higher scores indicate more severe incontinence. No between–group differences were noted in the Vaizey faecal incontinence scores. An improvement of around 1 unit was noted in both arms at 6 weeks, with a difference between arms of −0.1 (95% CI −1.3 to 1.0; *p* = 0.86). The improvement was maintained at 1 year, with a difference of −0.5 (95% CI −1.8 to 0.7; *p* = 0.38). A summary of these findings is presented in *Table 14* and *Figure 7*.

Pain

Haemorrhoidal pain was assessed by asking the patient to rate his/her pain related to haemorrhoids as of *today* and *over the last week*. Pain today was asked at baseline and again at days 1, 7 and 21, and, finally,

TABLE 14 Vaizey faecal incontinence scores

| Time point | Treatment group | | Difference (95% CI); *p*-value |
	RBL	HAL	
Randomisation			
n	84	88	
Mean (SD)	6.0 (5.3)	4.9 (4.6)	
Median (IQR)	4.0 (1.0–10.0)	4.0 (2.0–7.5)	
Baseline			
n	142	147	
Mean (SD)	5.9 (5.2)	5.3 (4.8)	
Median (IQR)	4.0 (1.0–9.0)	4.0 (2.0–8.0)	
6 weeks			
n	137	132	−0.1 (−1.3 to 1.0); 0.86
Mean (SD)	4.0 (4.5)	4.1 (4.9)	
Median (IQR)	3.0 (0.0–6.0)	3.0 (0.0–6.0)	
1 year			
n	118	107	−0.5 (−1.8 to 0.7); 0.38
Mean (SD)	4.0 (4.7)	4.5 (4.5)	
Median (IQR)	2.0 (0.0–6.0)	3.0 (1.0 –7.0)	

Mean difference is adjusted for age, gender, prior treatment and surgeon.
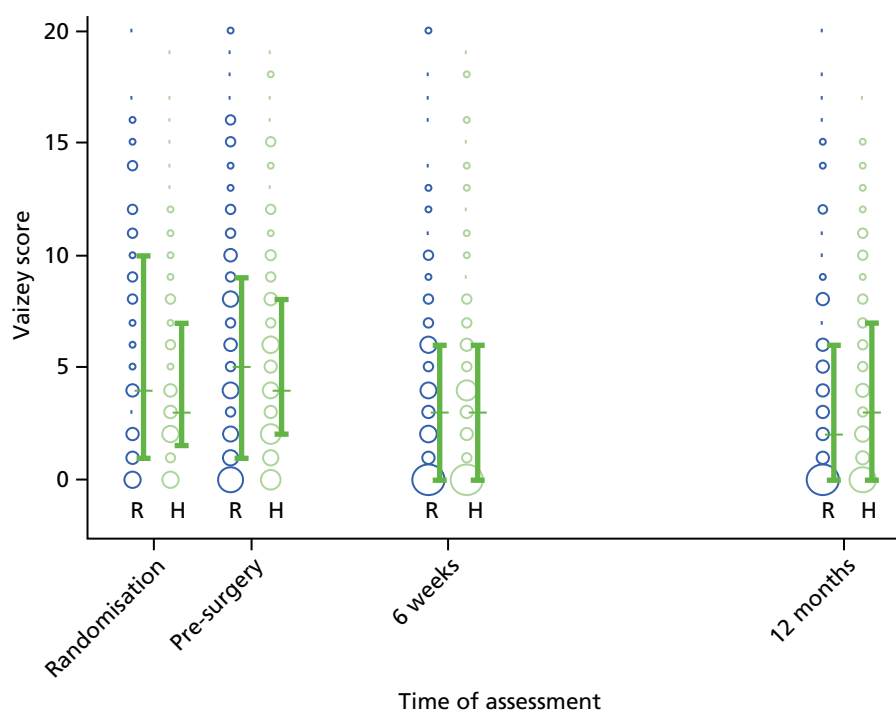
FIGURE 7 Vaizey faecal incontinence score. Note that the area of data points is proportional to the number of participants with that value. Vertical lines represent median and IQR.

at 6 weeks. Pain over the last week was asked at days 7 and 21, and, finally, at 6 weeks. Both of these are summarised in *Tables 15* and *16* and *Figures 8* and *9*; a score of '0' = 'no pain', whereas a score of '10' = 'worst imaginable pain'. The change in pain as recorded by VAS is shown in *Table 17*. Pain was

TABLE 15 Level of pain relating to haemorrhoids: pain experienced today

Time point	Treatment group		Difference (95% CI); *p*-value
	RBL	HAL	
Randomisation			
n	84	89	
Mean (SD)	2.4 (2.6)	2.3 (2.5)	
Median (IQR)	1.0 (0.0–4.0)	1.0 (0.0–3.3)	
Baseline			
n	148	150	
Mean (SD)	2.2 (2.5)	2.5 (2.7)	
Median (IQR)	1.0 (0.0–4.0)	1.0 (0.0–5.0)	
1 day			
n	162	140	−1.2 (−1.8 to −0.5); < 0.001
Mean (SD)	3.4 (2.8)	4.6 (2.8)	
Median (IQR)	3.0 (1.0–5.2)	5.0 (2.0–7.0)	
7 days			
n	157	133	−1.5 (−2.0 to −1.0); < 0.001
Mean (SD)	1.6 (2.3)	3.1 (2.4)	
Median (IQR)	1.0 (0.0–2.0)	3.0 (1.0–5.0)	

continued

TABLE 15 Level of pain relating to haemorrhoids: pain experienced today (*continued*)

Time point	Treatment group		Difference (95% CI); *p*-value
	RBL	HAL	
21 days			
n	151	129	–0.1 (–0.6 to 0.3); 0.44
Mean (SD)	1.3 (2.0)	1.4 (1.9)	
Median (IQR)	0.0 (0.0–2.0)	1.0 (0.0–2.0)	
6 weeks			
n	144	137	0.2 (–0.2 to 0.7); 0.32
Mean (SD)	1.2 (2.1)	1.0 (1.8)	
Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–1.0)	

TABLE 16 Level of pain relating to haemorrhoids: pain experienced over last week

Time point	Treatment group		Difference (95% CI); *p*-value
	RBL	HAL	
7 days			
n	157	133	–2.3 (–3.0 to –1.6); < 0.001
Mean (SD)	3.9 (3.2)	6.3 (2.9)	
Median (IQR)	3.0 (1.0–7.0)	7.0 (4.0–9.0)	
21 days			
n	151	129	–0.3 (–0.9 to 0.4); 0.38
Mean (SD)	2.1 (2.7)	2.4 (2.5)	
Median (IQR)	1.0 (0.0–4.0)	2.0 (0.0–3.0)	
6 weeks			
n	144	137	0.2 (–0.4 to 0.7); 0.56
Mean (SD)	1.7 (2.6)	1.6 (2.3)	
Median (IQR)	0.0 (0.0–3.0)	0.0 (0.0–2.0)	

Mean difference is adjusted for age, gender, prior treatment and surgeon.

TABLE 17 Change in VAS pain from baseline

Time point	Treatment group		Difference (95% CI); *p*-value
	RBL	HAL	
1 day			
n	160	136	–1.0 (–1.6 to –0.3); 0.007
Mean (SD)	1.1 (3.1)	2.1 (3.0)	
Median (IQR)	1 (0 to 3)	2 (0 to 4)	
More painful	90 (56%)	97 (71%)	
Same	34 (21%)	18 (13%)	
Less painful	36 (23%)	21 (15%)	

TABLE 17 Change in VAS pain from baseline (*continued*)

| Time point | Treatment group | | Difference (95% CI); *p*-value |
	RBL	HAL	
7 days			
n	155	129	−1.4 (−2.1 to −0.7); < 0.0001
Mean (SD)	−0.7 (2.9)	0.7 (2.8)	
Median (IQR)	0 (−2 to 0)	1 (0 to 2)	
More painful	38 (25%)	72 (56%)	
Same	48 (31%)	25 (19%)	
Less painful	69 (45%)	32 (25%)	
21 days			
n	149	127	−0.1 (−0.7 to −0.6); 0.880
Mean (SD)	−1.0 (2.9)	−1.0 (2.8)	
Median (IQR)	−1 (−2 to 0)	0 (−2 to 0)	
More painful	25 (17%)	26 (20%)	
Same	49 (33%)	45 (35%)	
Less painful	75 (50%)	56 (44%)	
6 weeks			
n	142	132	0.3 (−0.4 to 0.9); 0.410
Mean (SD)	−1.0 (2.9)	−1.3 (2.6)	
Median (IQR)	0 (−2 to 0)	−1 (−3 to 0)	
More painful	30 (21%)	16 (12%)	
Same	46 (32%)	48 (36%)	
Less painful	66 (46%)	68 (51%)	

Mean difference is adjusted for age, gender, prior treatment and surgeon.
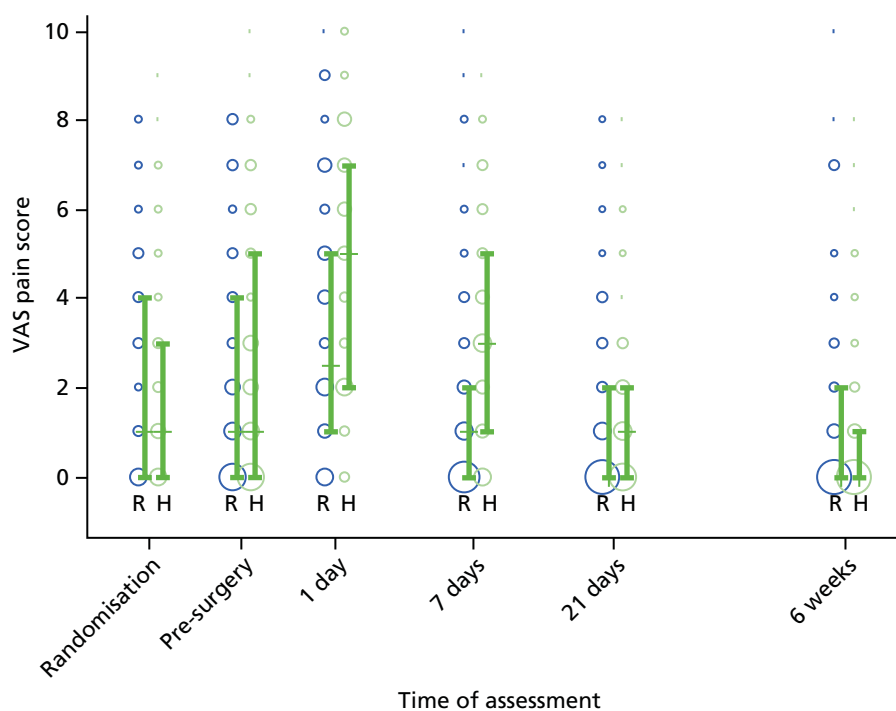
FIGURE 8 Visual analogue scale pain scores: pain today.
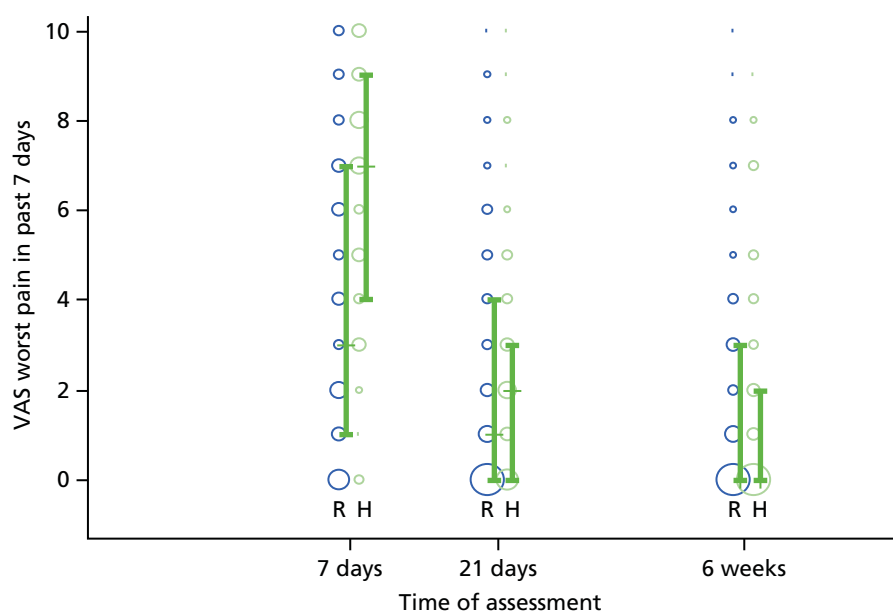
FIGURE 9 Visual analogue scale: pain over the last 7 days. Note that the area of data points is proportional to the number of participants with that value. Vertical lines represent median and IQR.

increased in the HAL group at one and seven days after the procedure, but the groups were similar at day 21 and at 6 weeks.

Clinical appearance of haemorrhoids at proctoscopy

Proctoscopy was conducted at the 6-week visit only if the patient reported continuing symptoms; proctoscopy was conducted more often in the RBL group. The data in *Table 18* show that, in the majority of patients in whom proctoscopy was conducted, the grade had reduced at 6 weeks, with a one-grade increase observed in only four patients in the RBL group and none in the HAL group.

All important harms or unintended effects in each group

A total of 15 individuals reported SAEs. One patient (in the RBL arm) experienced several episodes of bleeding following the procedure: further investigations revealed that the patient had a rectal tumour. This SAE was classified as pre-existing and is not included in *Table 19*. Of the remaining 14 SAEs, 12 followed HAL and two followed RBL. One of the participants had been randomised to the RBL arm

TABLE 18 Grade of haemorrhoids at 6 weeks and change from baseline

	Treatment group	
Grade	RBL (*n* = 48)	HAL (*n* = 27)
At week 6		
Grade I	9	12
Grade II	27	12
Grade III	12	3
Change from baseline to 6 weeks		
Grade III → I	5	4
Grade II → I or III → II	17	12
Unchanged	25	11
Grade II → III	4	0

TABLE 19 Serious adverse events by classification

SAE	Treatment group	
	RBL (*n* = 178)	HAL (*n* = 162)
Any SAE	*2 (1%)*	*12 (7%)*
Systemic complication	0	3 (2%)
Urinary retention	0	2 (1%)
Pelvic sepsis	0	1 (< 1%)
Other	2 (1%)	6 (4%)

but was switched over to HAL, but the summaries in *Table 19* are based on the treatment actually received and include all treated participants. All 14 events were expected.

Other complications, which were not classified as 'serious', included fissures, which occurred in 3 out of 143 (2%) of the HAL group and 0 out of 150 in the RBL group. There were no cases of fistula formation or anal stenosis in either group. At 6 weeks, 10 out of 143 (7%) of the HAL group and 10 out of 150 (7%) of the RBL group had evidence of anal skin tags.

Post hoc analyses

Some post hoc analyses have been discussed in previous sections [see *Recurrence (primary outcome)* regarding repeat RBL and recurrence, and see *Haemorrhoid Symptom Severity Score'* regarding Nyström's use of '0' or '1' on the symptoms scale being a signal of cure].

Pre-randomisation questionnaire
As previously mentioned, the baseline was originally measured prior to procedure as opposed to at randomisation. Following a recommendation from the DMEC, the protocol was subsequently amended to allow collection at both time points. The rationale for so doing was that self-reported severity may differ once the allocated treatment is known, thereby introducing an expectation bias. Specifically, participants randomised to the more intensive HAL surgery may rationalise their planned treatment by reporting higher levels of pain and discomfort than those randomised to receive RBL. Furthermore, it is possible that symptoms may change over time, which would also cause imbalance in pre-treatment values, as waiting time for HAL was longer than for RBL.

The agreement between pre-randomisation and pre-treatment values were therefore investigated among patients for whom data were available at both time points. The following are presented for each self-reported measure:

- The Bland–Altman plot for agreement within each treatment arm, together with the overall mean difference and 95% limits of agreement (also known as a 95% reference interval). The plot is the difference between pre-treatment and pre-randomisation (i.e. the change between the two) plotted against the average of the two. The 95% limits of agreement (also known as reference limits) for the difference were derived based on a normal distribution and quantify how closely the pre-randomisation and pre-treatment value agree. The average is plotted on the horizontal axis, which allows assessment of whether or not (dis)agreement varies according to severity.
- The difference between pre-treatment and pre-randomisation values against time elapsed between the two. The reference limits were the same as those produced for the Bland–Altman plot. Plotting the difference against elapsed time between the two measures allows an assessment of whether or not (dis)agreement increases with the time elapsed between the two measurements.

The agreement is displayed visually for each method in *Figures 10–13*. The difference and 95% limits of agreement are also summarised in *Table 20*, along with the difference between the two means and the ratio of their variances.

TABLE 20 Agreement between self-completed measures of symptoms, incontinence, EQ-5D-5L and pain pre-randomisation and pre-treatment

Measure	Treatment group, mean difference (95% agreement limits)		Difference in means (*p*-value)	Ratio of variances (*p*-value)
	HAL	RBL		
Haemorrhoid symptom score	0.0 (–3.0 to 3.0)	0.1 (–3.0 to 3.1)	–0.1 (0.823)	0. 96 (0.864)
EQ-5D-5L	–0.01 (–0.13 to 0.11)	–0.00 (–0.12 to 0.11)	–0.01 (0.508)	1.11 (0.691)
Vaizey faecal incontinence score	–0.1 (–5.6 to 5.3)	0.4 (–2.7 to 3.5)	–0.5 (0.231)	3.14 (< 0.001)
VAS pain	0.2 (–3.8 to 4.2)	–0.0 (–2.5 to 2.4)	0.2 (0.479)	2.63 (< 0.001)
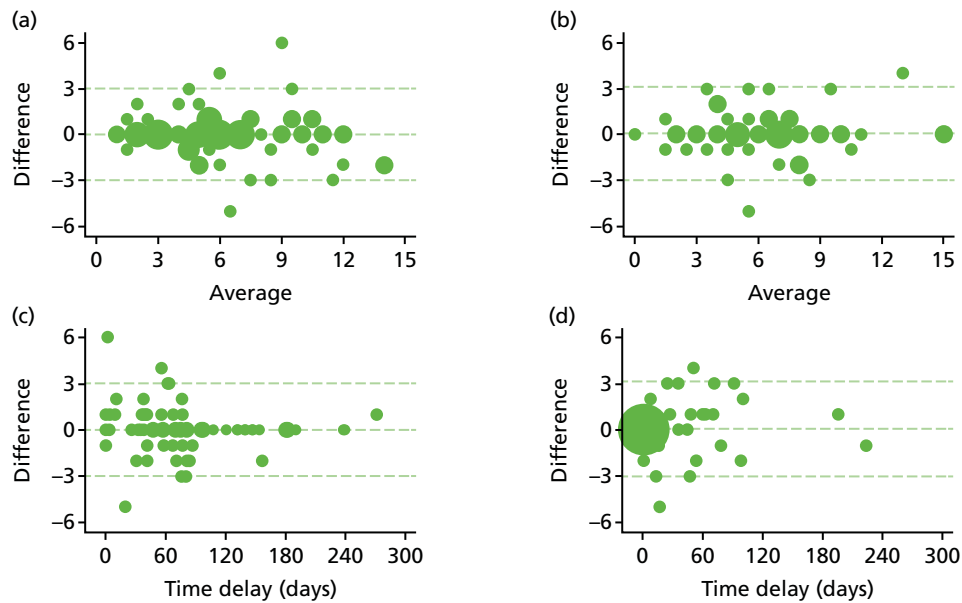
FIGURE 10 Agreement of haemorrhoid symptom severity scores at randomisation and pre-procedure. Bland–Altman graphs are given for (a) HAL and (b) RBL. Difference between the measures in relation to elapsed time between the two is given for (c) HAL and (d) RBL.
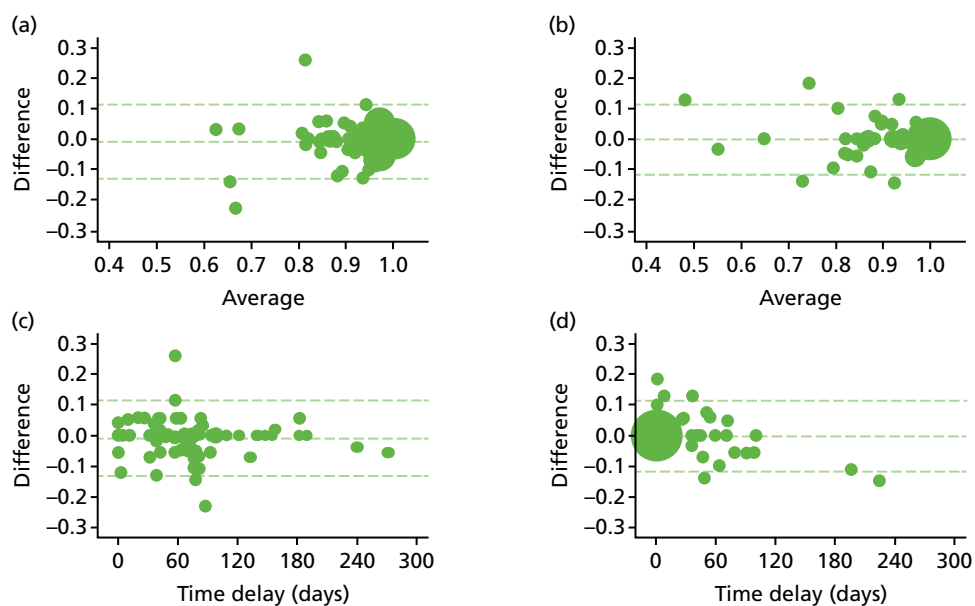
FIGURE 11 Agreement of EQ-5D-5L scores at randomisation and pre-procedure. Bland–Altman graphs are given for (a) HAL and (b) RBL. Difference between the measures in relation to elapsed time between the two is given for (c) HAL and (d) RBL.
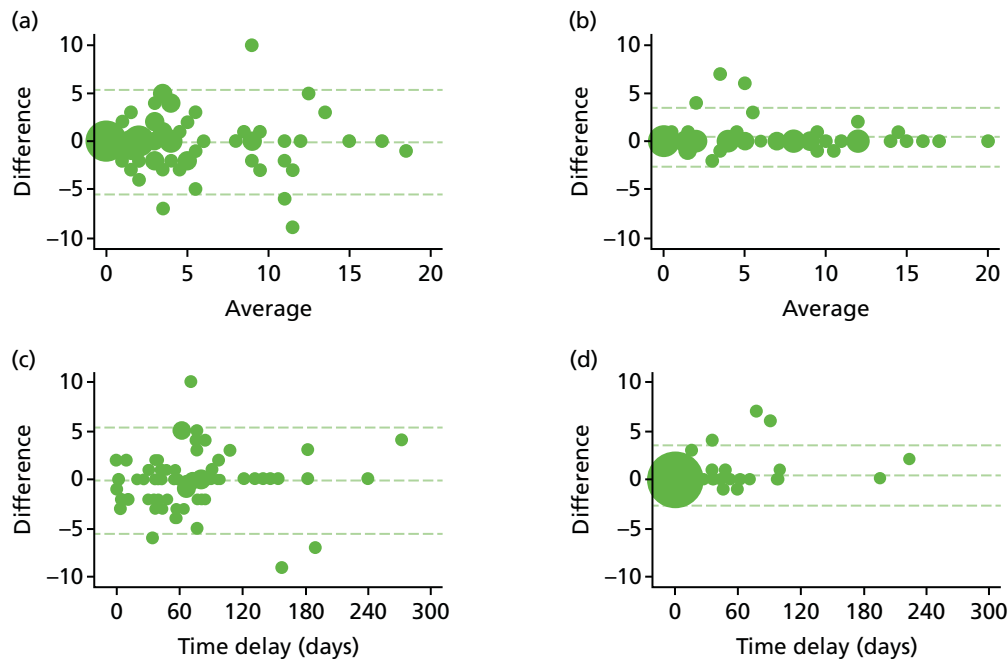
FIGURE 12 Agreement of Vaizey scores at randomisation and pre-procedure. Bland–Altman graphs are given for (a) HAL and (b) RBL. Difference between the measures in relation to elapsed time between the two is given for (c) HAL and (d) RBL.
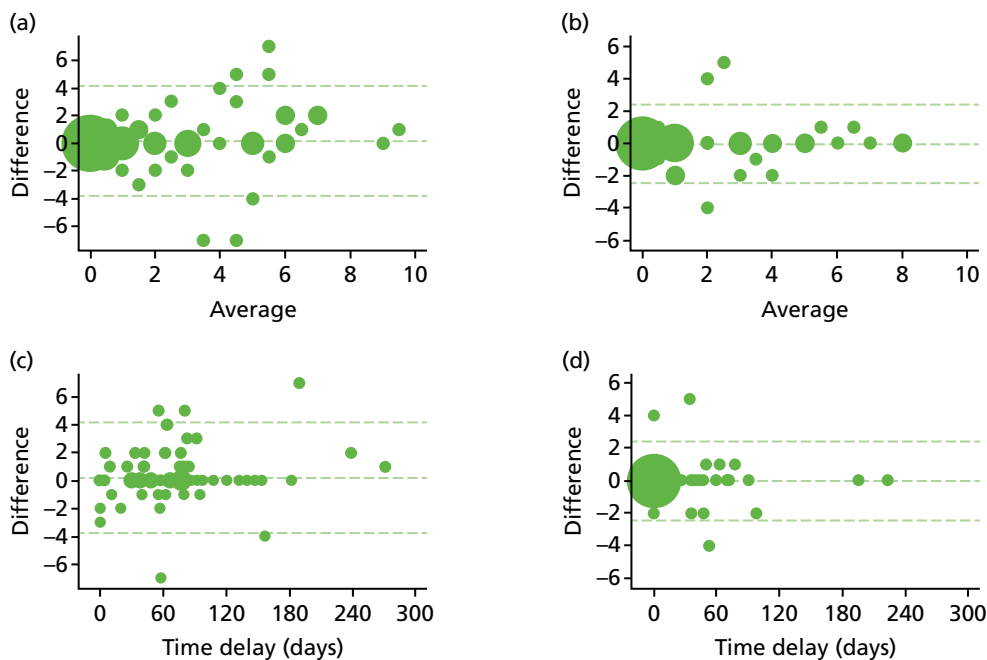
FIGURE 13 Agreement of VAS pain scores at randomisation and pre-procedure. Bland–Altman graphs are given for (a) HAL and (b) RBL. Difference between the measures in relation to elapsed time between the two is given for (c) HAL and (d) RBL.

Overall, the extent of agreement was generally similar regardless of the severity. For the VAS pain score, there was some indication that the pre-randomisation and pre-procedure time points were in closer agreement in the HAL arm than the RBL arm, as demonstrated by the ratio of the two variances (2.63; F-test $p < 0.001$). The same was also true for incontinence, as estimated by the Vaizey tool, where the difference between randomisation and procedure again tended to be greater in the HAL arm than the RBL arm (ratio of variances 3.14; $p < 0.001$). On the other hand, the two values differed less in the HAL arm for the EQ-5D 'thermometer' health state (ratio of variances 0.48; $p = 0.004$), although this may reflect a

handful of participants with outlying values. There was no indication of any systematic change (i.e. no consistent deterioration or spontaneous resolution between randomisation and procedure) on any measure.

Haemorrhoidal artery ligation device

Among participants undergoing HAL, the preferred surgical device appeared to be determined by site rather than participant characteristics. Five sites ($n = 73$) used the AMI HALO device on all participants, with the remaining 12 sites using the THD device in 87 cases and the HALO device in two. There was no significant difference in outcomes between the types of device, although fewer recurrences were seen in those in the THD arm (26% vs. 35%; adjusted OR 0.65, 95% CI 0.33 to 1.29; $p = 0.22$). Symptoms and pain were also similar for the two procedures, data are shown in *Table 21*. The Vaizey faecal incontinence score was higher for THD than HALO at 6 weeks (mean scores 5.2 vs. 3.2) and 1 year (means 5.6 vs. 3.5), but also prior to procedure (means scores 6.3 vs. 4.8). As a consequence, the magnitude of the difference at 6 weeks (mean difference = 2.0, 95% CI 0.5 to 3.6; $p = 0.01$) was greater than the change from baseline (mean difference incorporating an adjustment for baseline = 1.3, 95% CI –0.3 to 2.8; $p = 0.11$).

TABLE 21 Outcomes for the two HAL devices used in the trial

Measure: time point	Device HALO *n* (%) with recurrence	THD *n* (%) with recurrence	THD vs. HALO OR (95% CI); *p*-value
Recurrence			
6 weeks	5 (7)	8 (11)	2.23 (0.57 to 8.76); 0.250
1 year	26 (35)	23 (26)	0.65 (0.33 to 1.29); 0.221
	Mean (SD)	**Mean (SD)**	**Mean difference (95% CI); *p*-value**
Haemorrhoid Symptom Severity Score			
6 weeks	2.9 (2.7)	3.1 (3.3)	0.5 (–0.9 to 1.8); 0.493
1 year	3.5 (2.9)	3.8 (3.6)	0.0 (–1.1 to 1.2); 0.945
Pain (VAS)			
1 day	4.7 (2.9)	4.7 (2.9)	0.0 (–0.9 to 0.9); 0.957
7 days	3.3 (2.5)	2.9 (2.3)	–0.3 (–1.1 to 0.5); 0.415
21 days	1.5 (2.0)	1.4 (1.9)	–0.2 (–1.0 to 0.6); 0.586
6 weeks	0.9 (1.6)	1.0 (2.0)	0.1 (–0.5 to 0.8); 0.697
EQ-5D-5L			
1 day	0.78 (0.21)	0.73 (0.25)	–0.05 (–0.12 to 0.02); 0.131
7 days	0.83 (0.20)	0.83 (0.15)	0.00 (–0.06 to 0.05); 0.996
21 days	0.93 (0.10)	0.92 (0.13)	–0.00 (–0.05 to 0.04); 0.889
6 weeks	0.94 (0.13)	0.94 (0.09)	0.00 (–0.04 to 0.05); 0.829
1 year	0.92 (0.16)	0.90 (0.15)	–0.02 (–0.07 to 0.04); 0.575
Vaizey faecal incontinence symptom score			
6 weeks	3.2 (4.2)	5.2 (5.6)	2.0 (0.5 to 3.6); 0.010 1.3 (–0.3 to 2.8); 0.110[a]
1 year	3.5 (3.9)	5.6 (5.2)	1.0 (–1.0 to 3.0); 0.304

a Adjusted for baseline: means for THD device pre-procedure were higher than those for the HALO device (6.3 vs. 1.8).

Chapter 4　Health-economic results

Data completeness

Over the 12 months trial data collection period, data were missing for some participants for three key parameters used in the CEA: baseline utility, QALYs and total costs. The extent of missing data is presented in *Table 22*. The results of our descriptive analyses checks for missing data shows that the number of missing data is broadly similar across arms. For instance, the percentages of total costs missing were found to be 44.9% and 46.5% for RBL and HAL, respectively. These assessments were then used to inform the imputation model.

Costs

The mean total costs and their SD, skewness and CIs are reported descriptively, by group, in *Table 23*. These results are based on complete cases only and no imputation was performed at this stage. Similarly, the costs for each group of itemised resource use are presented in *Table 24*. The numbers of complete cases used for estimating the mean costs for each item and their percentages from the total number of participants per group are also reported. Figures in *Table 23* are for complete cases for every category (no missing for all cost categories), whereas figures in *Table 24* are the complete cases within each category. There is limited value of calculating and interpreting differences in mean costs at the level shown in *Table 24* because of missing data and non-adjustment for patient covariates at this level. The adjusted mean difference in costs for HAL compared with RBL was estimated using regression analysis and reported within the CUA results (see *Cost–utility analysis results*, below). However, *Table 24* shows the share of costs between different items, where the mean cost of further HAL procedure represents the highest share for the RBL group (£203.76), whereas the mean procedure cost is at the top for the HAL group (£732.56). The cost data are right-skewed, with only a few patients incurring very high costs in both arms of the trial. The histograms of cost data distribution for each group are shown in *Figures 14* and *15* for RBL and HAL, respectively.

TABLE 22 Data completeness for key parameters used in the CEA

Parameter	Treatment group, missing data: *n* (%)[a]		Difference in % missing	All participants (*N* = 372): *n* (%)[a]
	RBL (*n* = 187)	HAL (*n* = 185)		
Baseline utility	38 (20.3)	33 (17.8)	–2.5	71 (19.1)
QALYs	102 (–54.5)	93 (50.3)	–4.3	195 (52.4)
Total cost	84 (44.9)	86 (46.5)	1.6	170 (45.7)

a　The percentage shown for each arm is the percentage from the sample randomised to the treatment arm.

TABLE 23 Mean total costs of resource use for complete cases by group (unadjusted)

Treatment group	*n*	Mean costs (£)	SE	Skewness	95% CI
RBL	103	708.67	95.4	2.33	109 to 6000
HAL	99	1766.52	101.5	2.57	776 to 7014

TABLE 24 Mean costs of resource use for complete cases by group (unadjusted)

| | Treatment group | | | | | |
| | RBL | | | HAL | | |
Type of resource use	Mean costs (£)	SD	n (%)	Mean costs (£)	SD	n (%)
Medications	2.04	8.4	187 (100)	7.59	8.4	185 (100)
RBL procedure	109.00	0.0	187 (100)	0.00	0.0	185 (100)
Excisional tag removal	0.00	0.0	187 (100)	10.02	31.6	185 (100)
HAL procedure	0.00	0.0	179 (96)	732.56	299.7	151 (82)
Admissions for surgery	0.00	0.0	187 (100)	23.01	80.5	158 (85)
Proctoscopy	5.02	5.5	149 (80)	4.71	5.5	140 (76)
Other elective procedure	0.00	0.0	187 (100)	7.23	98.4	185 (100)
Post-discharge admissions	41.73	253.0	150 (80)	65.66	314.9	143 (77)
Other procedures	0.00	0.0	150 (80)	0.76	9.1	143 (77)
Repeated RBL	82.45	276.3	187 (100)	32.05	148.0	185 (100)
Further HAL	203.76	587.6	187 (100)	18.72	179.6	185 (100)
EH	16.14	155.6	187 (100)	24.47	191.1	185 (100)
SH	26.51	255.6	187 (100)	0.00	0.0	185 (100)
RBL in theatre	21.47	218.4	187 (100)	14.47	138.8	185 (100)
Admissions in 1 year	17.78	166.4	176 (94)	68.04	320.1	161 (87)
Emergency procedure	29.53	284.8	187 (100)	29.85	286.3	185 (100)
Consultant visits	88.59	131.2	175 (94)	86.39	151.2	161 (87)
GP visits	10.93	27.8	122 (65)	16.54	35.2	114 (62)
Nurse visits	0.56	6.2	122 (65)	0.85	3.8	113 (61)
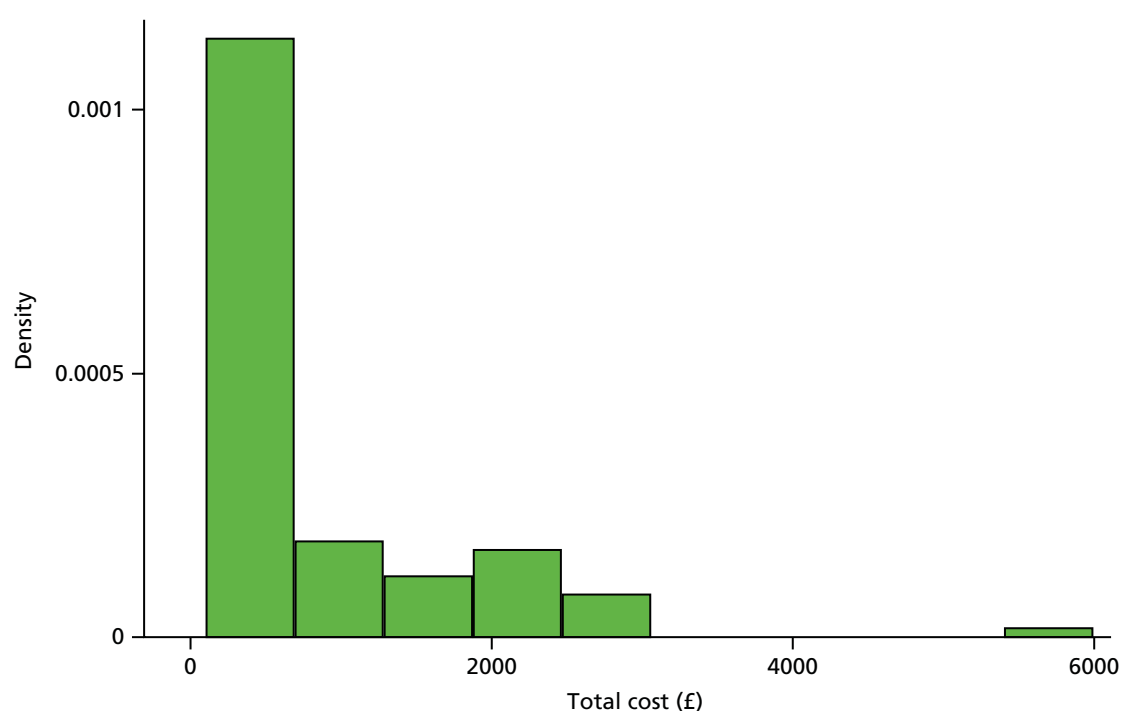
FIGURE 14 Distribution of cost data: RBL.
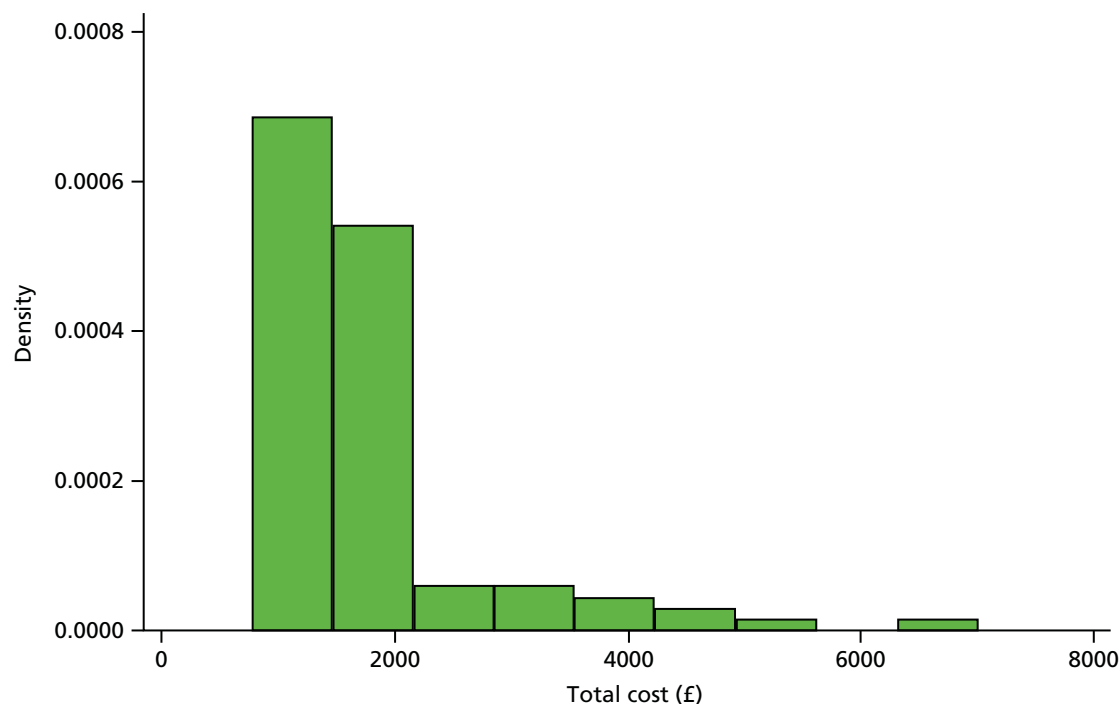
FIGURE 15 Distribution of cost data: HAL.

Outcomes

We examined the relationship between EQ-5D-5L and the haemorrhoids symptom score in order to validate the use of EQ-5D-5L as an outcome measure in the economic evaluation. *Figure 16* plots the mean symptom scores and mean EQ-5D-5L utility scores for all participants and visits for both the observed data, and the fit from a simple linear regression (controlling for age). The plot shows that symptom score is closely related to EQ-5D-5L, with a unit increase on the 15-point symptom score corresponding to an approximate 0.02 reduction in the EQ-5D-5L.
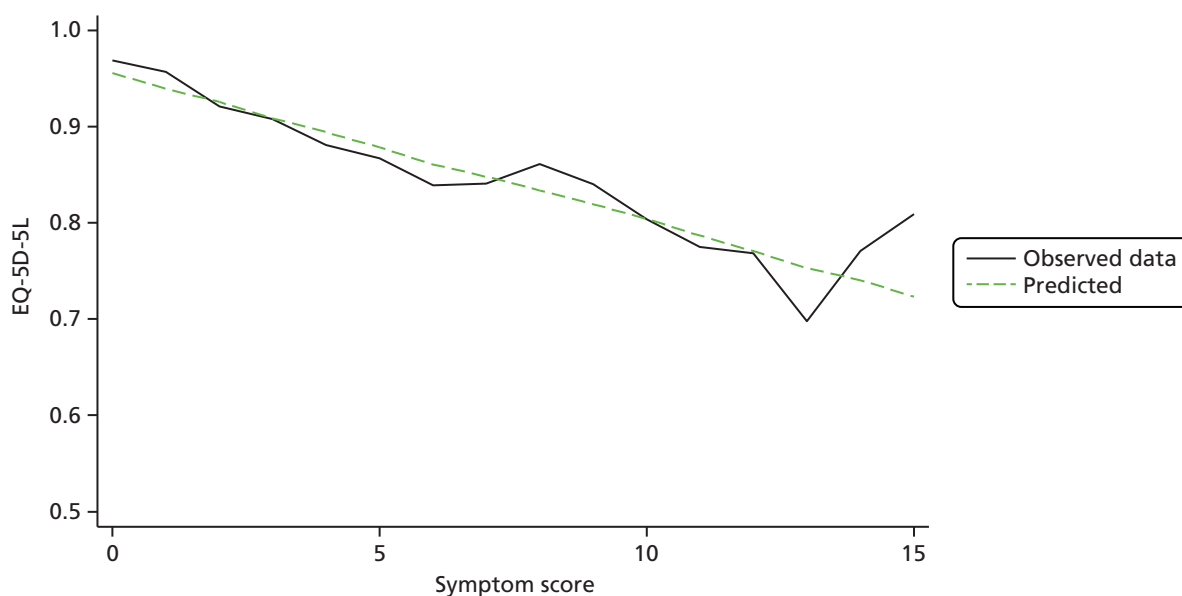
FIGURE 16 Symptom score vs. EQ-5D-5L.

The mean baseline utility and QALYs for RBL and HAL and mean differences with their SDs and CIs are reported in *Table 25*. The trend of EQ-5D-5L score baseline and subsequent follow-up over 12 months' time horizon (1 day, 1 week, 3 weeks, 6 weeks and 12 months) for both RBL and HAL for complete cases is shown in *Figure 17*. The EQ-5D-5L scores for each time points are descriptively reported above [see *European Quality of Life-5 Dimensions (5-level version)*].

Cost–utility analysis results

The ICER estimate from our primary analysis, which was based on imputed data, was £104,427 per QALY gained. The estimated differential costs, and differential QALYs and their SE, *p*-value and CIs are reported in *Table 26*. The mean difference in total cost is £1027 (95% CI £782 to £1272) for the HAL group compared with RBL (*p* < 0.001). However, the difference in QALYs – controlling for baseline utility – is very small (0.01, 95% CI –0.02 to 0.04) and not statistically significant (*p* = 0.49). The mean total cost of HAL was £1750 (95% CI £1333 to £2167) compared with £723 (95% CI £551 to £896) for RBL based on imputed data. The correlation of the residuals in the costs and effectiveness (QALY) equations from the SUR regression was 0.1063 and not statistically significant (*p* = 0.246). The full regression results are provided in *Appendix 3*.

TABLE 25 Descriptive statistics for baseline utility and QALYs

Parameter	Treatment group										Difference in means	t
	RBL					**HAL**						
	n	**Mean**	**SD**	**Min.**	**Max.**	*n*	**Mean**	**SD**	**Min.**	**Max.**		
Baseline utility	149	0.90	0.12	0.26	1	152	0.89	0.15	–0.07	1	–0.01	–0.617
QALYs	85	0.91	0.01	0.88	0.93	92	0.91	0.01	0.88	0.94	0.004	0.180

Max., maximum; Min., minimum.
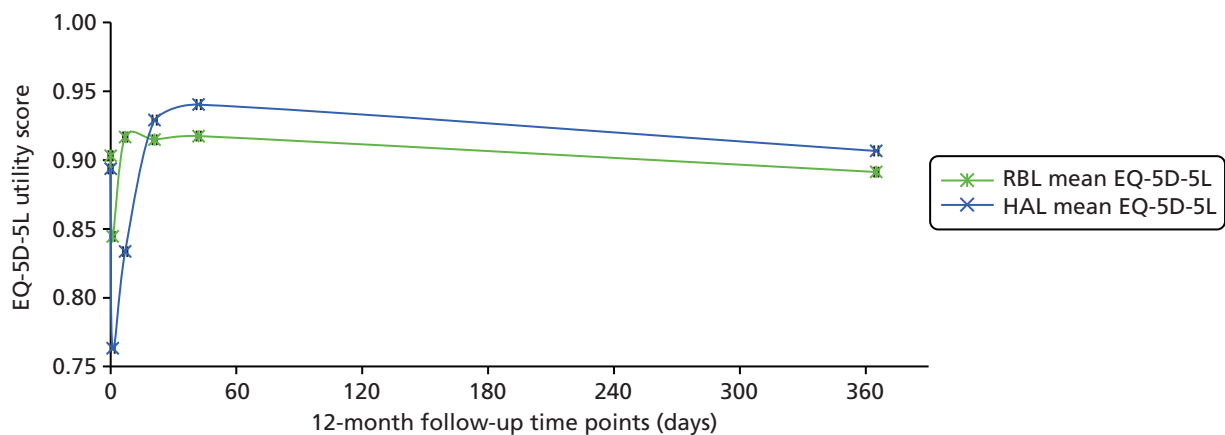
FIGURE 17 Mean EQ-5D-5L scores over 12 months' follow-up.

TABLE 26 Differential cost and differential QALYs based on SUR (HAL vs. RBL)

Outcome	Differential mean	SE	t	*p*-value	95% CI
Costs (£)	1027	124	8.25	< 0.001	782 to 1272
QALYs[a]	0.01	0.014	0.69	0.489	–0.02 to 0.04

a Controlling for base-line utility as a covariate in the QALY regression equation.

The CEAC curve generated from the parametric analysis, applied on imputed data, is presented in *Figure 18*. This graph shows the probability that the HAL procedure is cost-effective under a range of values for the cost-effectiveness threshold. At £20,000 per QALY threshold, HAL has zero probability of being cost-effective; at £30,000 threshold it has 0.05 probability of cost-effectiveness.

The confidence ellipses graph shown in *Figure 19* represents the ICER point estimate in the cost-effectiveness plane, with 50%, 75% and 95% CIs around the point estimate. As can be seen, the ICER point estimate falls in the north-east quadrant of the cost-effectiveness plane, suggesting that HAL is more costly and more effective than RBL procedure. However, the incremental QALY is very small and the confidence ellipses cross the vertical zero line, indicating that we are less confident that incremental QALY is positive.
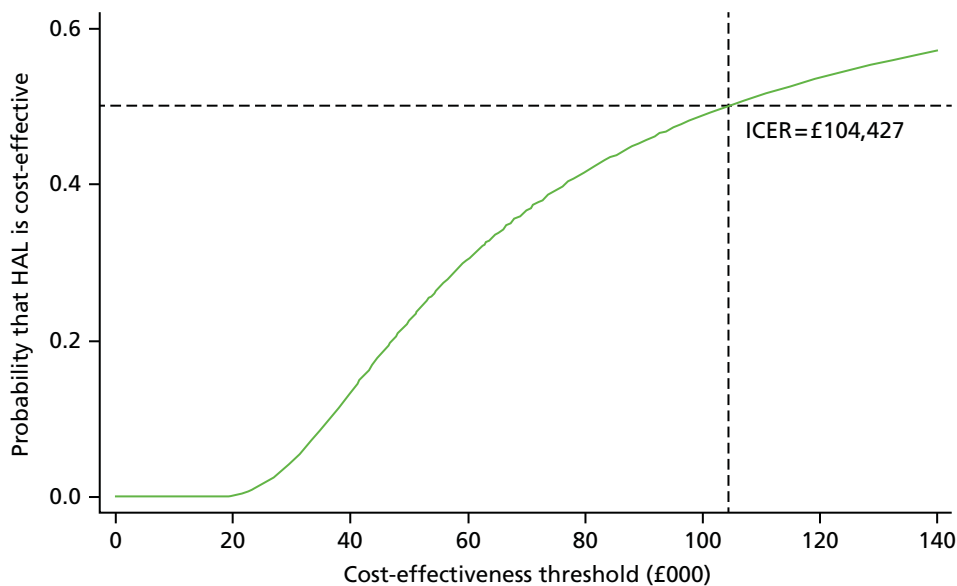
FIGURE 18 Cost-effectiveness acceptability curve showing the probability that HAL is cost-effective given different values of cost-effectiveness threshold.
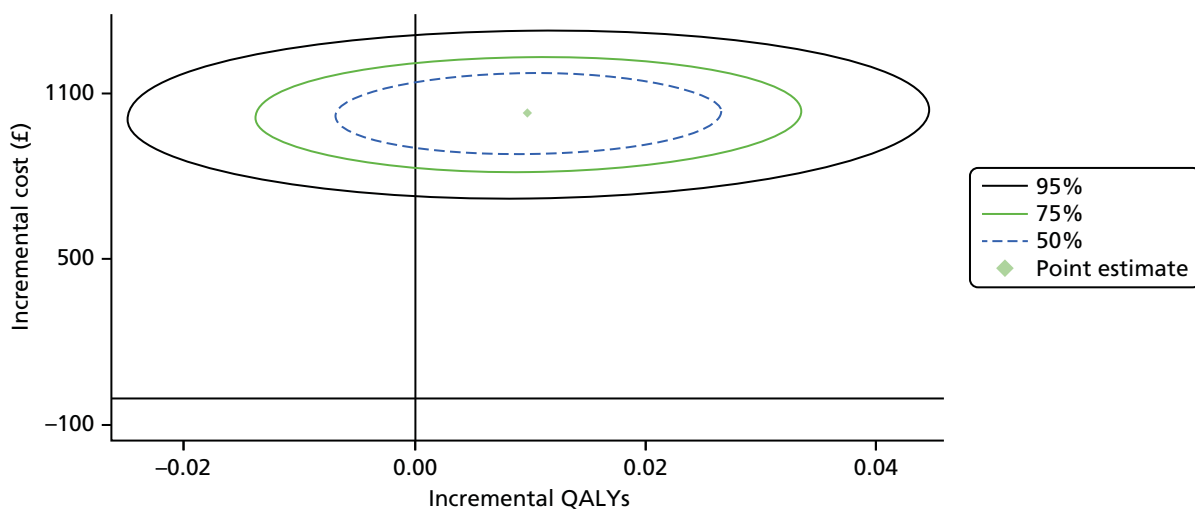
FIGURE 19 Cost-effectiveness confidence ellipses illustrating the ICER point estimate and CIs.

Figure 20 illustrates the incremental net monetary benefit (NMB) line with CI, which shows the same information around uncertainty in a different way. In this NMB approach, the incremental QALYs were converted into monetary terms using the upper bound of NICE cost-effectiveness threshold of £30,000 per QALY. As shown in *Figure 20*, if the policy-maker is willing to pay £104,427 per QALY gained from introducing the HAL procedure then the NMB would be zero, with similar degrees of uncertainty around this estimate to be either a positive or a negative value.

Result of subgroup analysis

Results from the subgroup analysis performed on (1) new patients and (2) patients with recurrence following RBL are presented in *Figure 21*. The ICER estimated for the subgroup of patients with recurrence following RBL before randomisation is higher than for new patients by £156,987. This result suggests that the generated QALY gains are more costly for patients with recurrence following RBL (before randomisation) than for new patients. This is mainly driven by a smaller difference in QALYs for patients with recurrence. For patients with recurrence following RBL, the mean difference in costs was £1091 (95% CI £623 to £1558; $p < 0.001$). The mean difference in QALYs was 0.004 (95% CI –0.049 to 0.058; $p = 0.870$). For new patients, the mean difference in costs was £1008 (95% CI £729 to £1286; $p < 0.001$). The mean difference in QALYs was 0.011 (95% CI –0.020 to 0.042); $p = 0.479$. See *Appendix 3* for the full regression results.

Cost-effectiveness results

The incremental cost per recurrence avoided is estimated to be £4882 (95% CI £3628 to £6135). This result, based on a derived estimate, shows that RBL groups had 87 (49.43%) recurrences compared with 48 (30%) recurrences for HAL groups [for details on clinical effectiveness, see *Recurrence (Primary Outcome)*, above]. When a sensitivity analysis based on recurrence from the consultants' questionnaire was completed for 1-year follow-up, the estimates of recurrence were 45 (25.6%), for the RBL group recurrences compared with 15 (9.4%) recurrences for HAL group. The incremental cost per recurrence avoided was estimated to be £6346 (95% CI £4417 to £7975) when recurrence reported by the consultant was considered.
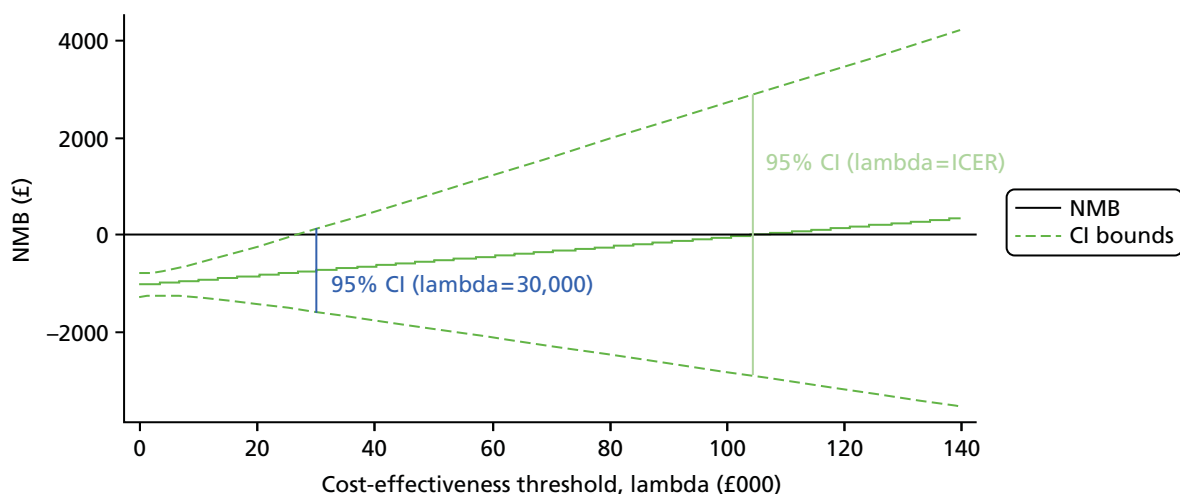
FIGURE 20 Net monetary benefit line with CIs at different values of cost-effectiveness threshold. Difference in mean costs = 1027; difference in mean QALYs = 0.01; SE of the mean differential costs = 124; SE of the mean differential QALYs = 0.014; covariance between costs and QALYs = 0.0443.

(a)

(b)
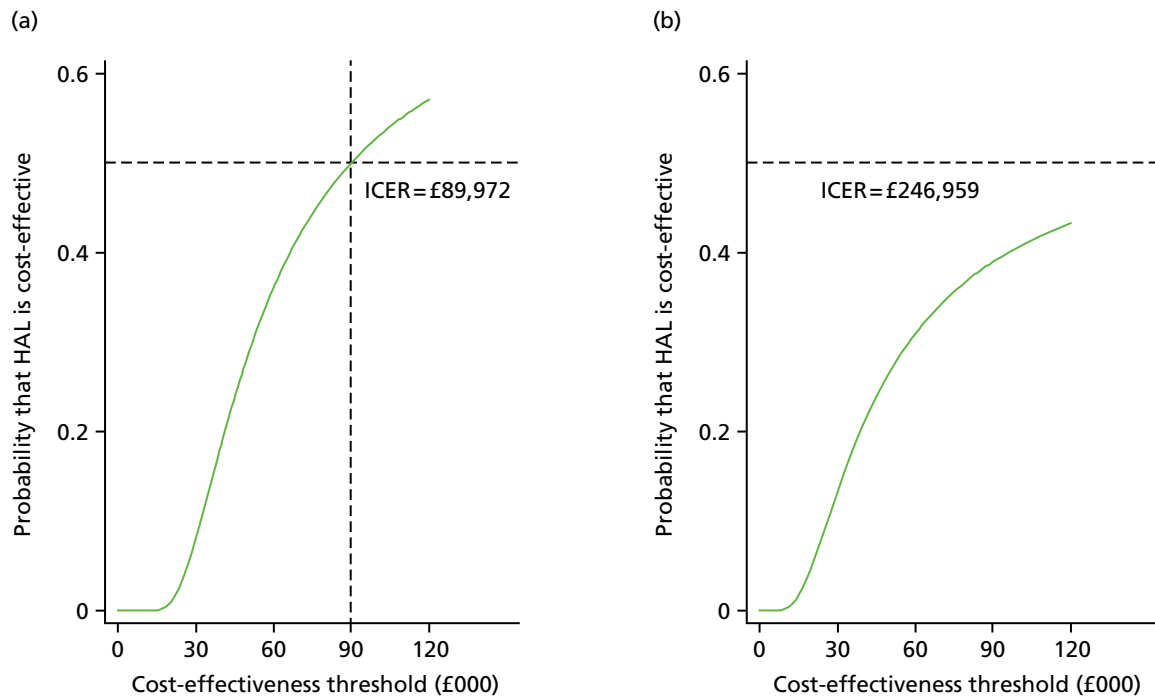
FIGURE 21 Subgroup analysis illustrated by combined CEAC curves.

Sensitivity analysis

Using the NHS reference cost for the HAL procedure, rather than the microcosting approach, made a difference of £48,052 per QALY to the base-case ICER estimate. The ICER for this scenario was estimated to be £152,479 per QALY, compared with £104,427 per QALY as estimated in our base-case analysis. However, the cost-effectiveness results remained similar: HAL is highly unlikely to be cost-effective at a maximum threshold of £30,000 per QALY. The results from this sensitivity analysis are presented in *Figure 22*. The regression results from this sensitivity analysis show that the mean difference in costs was £1498 (95% CI £1262 to £1735; $p < 0.001$). The mean difference in QALYs was 0.01 (95% CI –0.018 to 0.038; $p = 0.489$). The full regression results for all sensitivity analyses and model specifications are provided in *Appendix 3*.
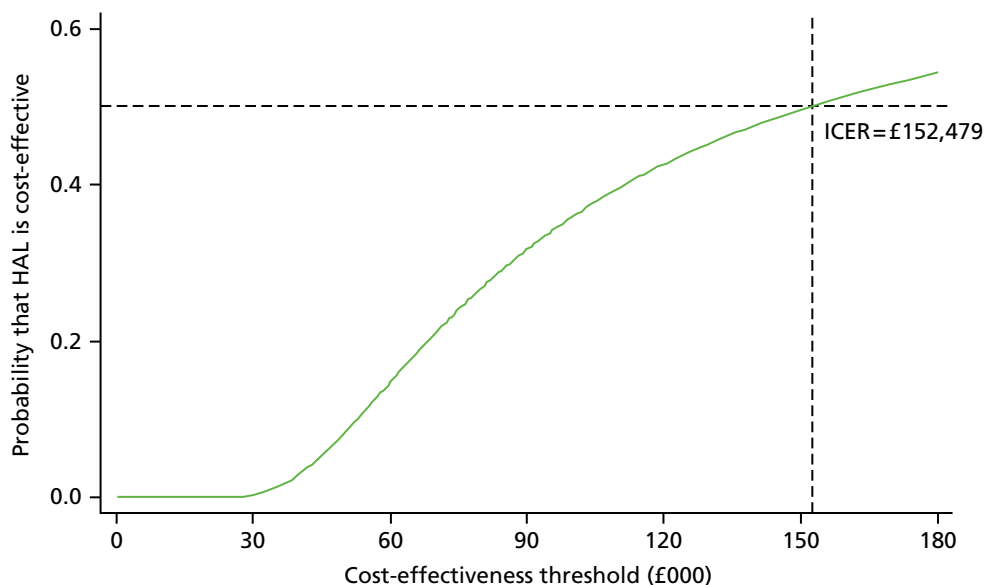
FIGURE 22 Sensitivity analysis using the NHS reference cost for the HAL procedure.

Our sensitivity analysis, when controlling for the grade of haemorrhoids, resulted in an ICER of £108,478 per QALY. This result shows the interaction with cost-effectiveness of HAL compared with RBL is conditional on grade III haemorrhoids. The regression results from this sensitivity analysis show that the mean difference in costs was £999 (95% CI £760 to £1239; p-value < 0.001). The mean difference in QALYs was 0.009 (95% CI –0.019 to 0.037; $p = 0.518$).

The CUA estimates from complete-case analysis using SUR model and controlling for baseline utility are presented in *Table 27*. The ICER estimate for this scenario is £90,688 per QALY gained. The correlation between cost and QALYs based on the Breusch–Pagan test of independence is reported in *Table 27*: this shows that cost and QALYs are positively correlated in this study, although this correlation was not statistically significant.

The results from the sensitivity analysis applying an estimated utility decrement for each subsequent procedure did not materially change the cost-effectiveness result. From this analysis, the mean difference in cost was £1030 (95% CI £760 to £1300; $p < 0.001$). The mean difference in QALYs was 0.008 (95% CI –0.020 to 0.036; $p = 0.562$), leading to an ICER of £125,076 per QALY gained. See *Appendix 3* for full regression results.

Long-term cost-effectiveness

Results from the long-term CUA for HAL compared with RBL over a 4-year time horizon generated incremental costs of £1117 and incremental QALYs of 0.051, leading to an ICER of £21,887. *Table 28* shows the deterministic cost-effectiveness result for the long-term extrapolation analysis. This result indicates that HAL remains not cost-effective at a £20,000 per QALY threshold.

The PSAs resulted in a mean difference in cost of £1125 for HAL compared with RBL, and mean difference in QALYs of 0.052, and, when combined together, led to an ICER of 21,798 per QALY gained. The probability of HAL being cost-effective at a £20,000 threshold from the long-term analysis was 0.34. *Figure 23* shows the joint distribution and the uncertainty around costs and QALYs estimated from the extrapolation analyses. Each point represents a possible ICER estimate, with 1000 points estimated from the PSA simulations. There are high levels of uncertainty around both costs and QALYs, with QALYs being the most uncertain estimates. Therefore, the long-term results should be interpreted with caution. This was mainly driven by the quality of evidence on long-term recurrence, particularly for HAL.

TABLE 27 Sensitivity analysis: CUA for complete-case analysis using SUR and controlling for baseline utility

Outcome	Differential mean	SE	z	*p*-value	95% CI
Costs (£)	1073	190	5.63	< 0.001	700 to 1447
QALYs[a]	0.01	0.015	0.68	0.495	–0.02 to 0.04

a Controlling for baseline utility as a covariate in the QALY regression equation.
Correlation between costs and QALYs = 0.1063 ($p = 0.246$).

TABLE 28 Deterministic long-term cost-effectiveness results

Outcome	Treatment group		Mean difference	ICER (£)
	RBL	HAL		
Costs (£)	1205	2322	1117	
QALYs	3.4807	3.5317	0.0510	21,887
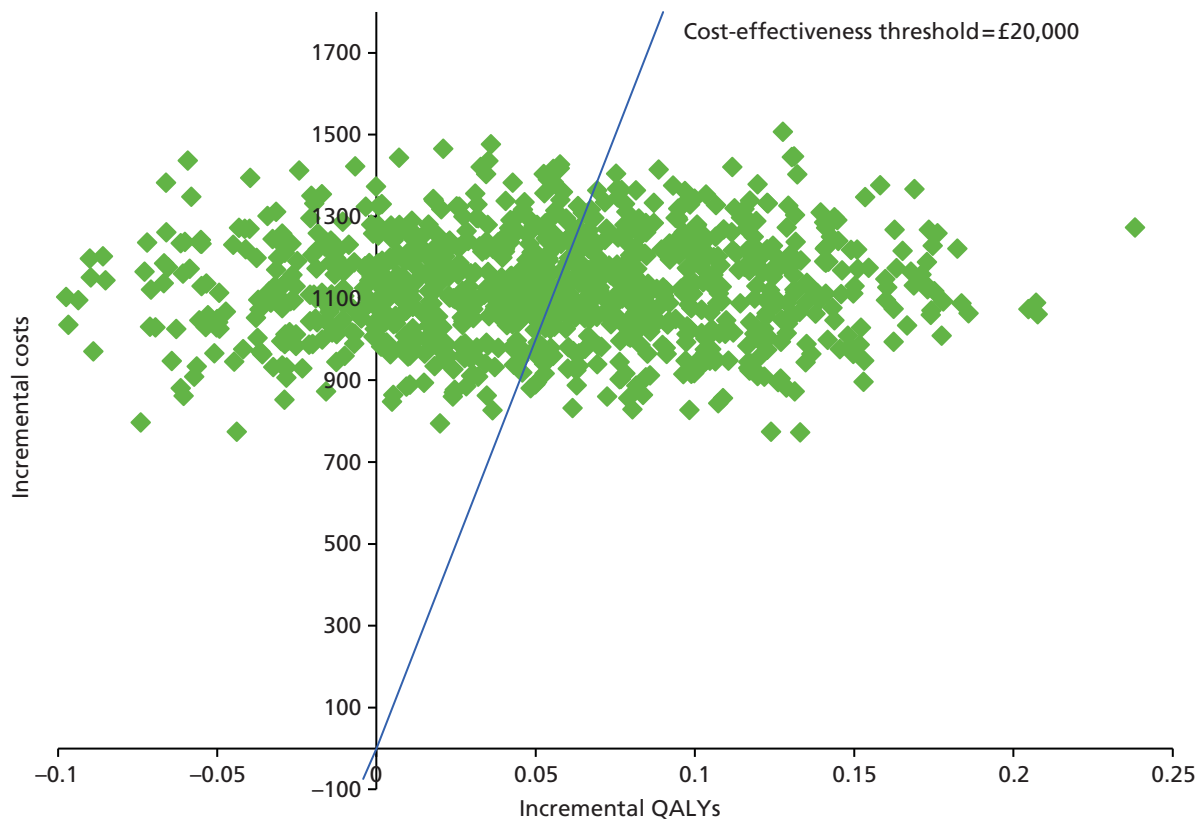
FIGURE 23 Uncertainties in the mean difference in costs and QALYs from long-term CEA.

Summary

The main findings from the within-trial CUA suggests that the HAL procedure is highly unlikely to be cost-effective compared with RBL. In the base-case results, the difference in mean total costs was £1027 higher for HAL than RBL. QALYs were higher for HAL but the difference was very small (0.01), resulting in an ICER of £104,427 per additional QALY.

The base-case CEA suggests that the incremental cost per recurrence avoided was estimated £4882. In a sensitivity analysis scenario using the derived recurrence, the incremental cost per recurrence avoided was estimated to be £6346.

Chapter 5 Discussion

Main findings

Primary outcome: recurrence

Haemorrhoidal disease is a benign condition and, as such, treatment is primarily aimed at addressing the patient's symptoms. In the absence of a validated symptom scoring system, we felt that the most important determinant of treatment success was patient-reported outcome. This was supported by a robust patient and public involvement (PPI) exercise carried out during the design of the trial. Clinical experience tells us that the physical appearance of the anal cushions post-haemorrhoid treatment correlates poorly with patients' symptoms, meaning that anorectal visualisation is not a reliable surrogate of success. We therefore used a simple, dichotomised definition of recurrence as described by Shanmugam et al.[6,51] and measured this at 12 months post intervention. Using this patient-reported outcome alone, there was no difference in recurrence between the groups at 12 months. However, a number of patients (particularly those who underwent RBL) had undergone a further intervention for haemorrhoid symptoms within the 12 months, indicating that any symptomatic relief had been achieved only by further corrective procedures. Classing these patients as recurrence, the rate for HAL was significantly lower than for RBL (30% vs. 49%; $p = 0.001$) at 12 months.

The overall level of recurrence following HAL was higher than the pooled rates reported in two systematic reviews, which were 11%[19] and 17.5%.[5] However, it should be noted that the recurrence rate among the constituent studies varied considerably and ranged up to 60%.[64] Similarly, reported recurrence rates for RBL also vary widely in the literature, ranging from 11% to > 50%.[6–11] This range can be attributed to many factors, but the most pertinent is probably the difficulty in defining exactly what constitutes recurrence. Some studies rely on clinical examination and patient-reported symptoms,[22,25,27,51,64] whereas others rely solely on symptomatology.[24,32] When considering symptoms only, some investigators consider a patient to be recurrence free when they have no perianal symptoms at all, whereas others consider this simply an improvement. A classic example of variation dependent on definition is provided by one study[64] reporting a very high recurrence rate of 60% at 30 months after a HAL procedure. However, the investigators report that, at the same time point, 86% of patients described a significant improvement in symptoms.

We adopted the more pragmatic approach[6] described above in which the patient's perception of symptomatic improvement was combined with the requirement that no further procedures were required in order to achieve a non-recurrence at 12 months. There were some practical hurdles to overcome when obtaining these data: a patient may have indicated that he/she was cured but could have forgotten about a consult or further treatment in the 12-month period since initial surgery, or a patient may have indicated recurrence when the 'recurrence' related to a residual skin tag[65] or an alternative diagnosis clearly documented by GP or consultant records. To address these issues, we used a combination of patient-reported assessment with GP and hospital consultant perception. A decision tree was developed and followed independently by two assessors who were blinded to the intervention, with consensus reached on any areas of disagreement. This ensured fidelity and we felt this resulted in the most accurate assessment of true recurrence that was possible.

Other factors that influence the recurrence rate include the duration of follow-up and the pre-treatment haemorrhoidal grade. We chose to assess recurrence at 12 months because published data suggest that most HAL and RBL recurrences occur within 1 year.[26] Several studies have shown that using HAL for higher-grade haemorrhoids or significant prolapse adversely affects the recurrence rate;[19,37,41,66,67] they also conclude that HAL is perhaps most effective for grade II and early grade III disease. We therefore limited our trial to this most clinically relevant patient population. As RBL is also most effective for this stage of disease, it was chosen as our comparator (see below).

Linked with recurrence is the need for further treatment. This was required in 31% of the RBL group and 15% of the HAL group. Eighteen per cent of the RBL group required a required further banding, the vast majority needing only one further procedure. It is common practice to repeat banding as part of a continuum of treatment in some patients with persistent symptoms, and it could be considered that these patients were actually treatment successes if by the end of the year they were cured or improved. Given that RBL is a quick, minimally invasive office procedure in comparison with HAL, it seems clinically relevant and reflective of actual practice to consider it as a 'course' of treatment as opposed to a single intervention. Including these patients as treatment success resulted in a reduction of the recurrence rate for the RBL arm from 49% to 37.5%, which was not statistically different from the HAL arm.

Secondary outcomes

Recurrence at 6 weeks

When we examined persistent significant symptoms at 6 weeks (i.e. immediate failure of treatment), the rates were significantly lower than at 1 year in both groups (HAL 9% vs. 30%; RBL 29% vs. 49%); 13 out of 143 (9%) patients in the HAL group and 44 out of 150 (29%) patients in the RBL group ($p < 0.001$) had persistent symptoms at this time point. The large increase in numbers of recurrences, in both groups after 1 year, suggests significant symptom deterioration. It is not clear when the deterioration ends. A prolonged follow-up would be relevant to see if further attrition continues, although current data suggest that most HAL recurrences occur within the year.[26]

Symptom severity score

Rubber band ligation and HAL both appeared to improve symptoms, with the improvement at 6 weeks being larger for HAL than RBL. The mean improvements on the 15-point haemorrhoidal symptom severity questionnaire were 3.4 points for HAL and 2.5 for RBL at 6 weeks, with an adjusted mean difference of 1.0 (95% 0.3 to 1.8; $p = 0.01$). Patient's self-assessed reported symptoms remained lower at 1 year, but the difference between groups was not maintained at this time point.

The improvement after both interventions was more modest than the one reported in the Nyström study,[42] for which a difference of about 6 points was observed in patients who were undergoing both haemorrhoidectomy and SH. However, in this study the preoperative score was higher than in our study, reflecting their criteria being grade III or IV haemorrhoids.

Applying Nyström et al.'s[42] definition of cure as 0–1 point on the haemorrhoid symptom severity score, there was no difference between the two interventions at either 6 weeks or 1 year. Indeed it is striking how few patients reported a 0–1 symptom score despite considering themselves to be cured or improved according to our primary outcome measure (about one-third from each group). This suggests that many patients are not concerned with a certain level of persistent symptoms related to haemorrhoids, and may suggest that symptom severity scores need to take into account further information. This is consistent with a trial[68] from general practice, in France, for which targeted questionnaires were given to all patients who were attending over a 2.5-day period. Only 2% were seen primarily with anal symptoms but the targeted questionnaire suggested that 14% had potential haemorrhoidal symptoms. Perhaps a more lenient cut-off point is required. It should be noted that the design of the trial means that assessment at 1 year did not take into account the fact that some patients required a repeat procedure to achieve this level of relief.

Health-related quality of life

As mentioned previously, haemorrhoidal disease is a benign condition and, as such, intervention is essentially aimed at improving QoL, making this is an important indicator of success. This is particularly pertinent as haemorrhoids can affect a relatively young, professionally active population.

Our results suggest that the majority of patients had an improvement in their QoL above baseline after intervention but that improvement was the same for both interventions after day 21. Before this date there was a difference in favour of RBL, probably related to the fact that the HAL procedure was more painful

and this pain lasted longer. Although no long-term difference was seen between the two groups, it is important to note that both procedures did result in an improved QoL score. In other words, both interventions appear worthwhile from a QoL perspective. The alternative management option of simply reassuring that there is no sinister cause to patients' symptoms and giving general lifestyle advice (as many have poor bowel habit) may not be appropriate.[69]

Continence

A common symptom of haemorrhoidal disease, particularly when prolapse is present, is persistent soiling. Anal tone maintains continence and the majority of this resting tone comes from the action of the internal (and some external) sphincter. However, muscle tone alone is insufficient to provide a complete hermetic seal around the anal canal and there is therefore a contribution from the haemorrhoidal tissue. It follows that disruption of this tissue in the form of anal prolapse will lead to inefficiencies in this hermetic seal and leakage of faecal matter. This registers as varying levels of faecal incontinence and soiling.

Our results are consistent with this: at baseline the majority of participants from both groups had either no incontinence or very mild incontinence. Correction of the prolapse would be expected to result in a reduction in soiling and hence Vaizey score. This was, indeed, the case, in that there was a small reduction in the mean score of 1–2 points after both interventions. There was no difference in continence score between the two interventions.

From the literature, a small proportion of patients has reported incontinence following both procedures. The mechanism of this worsening incontinence is not clear. Pre-existing sphincter compromise may often exist with haemorrhoidal disease, particularly prolapse. It may be that, in these patients, the contribution form the haemorrhoids towards anal tone is essential for continence. Reduction of the haemorrhoidal bulk unmasks the pre-existing anal sphincter dysfunction. Whatever the reason, the proportion of patients who deteriorated after intervention was similar in both groups.

Pain

Our data indicate that patients report increased pain following both procedures (56% RBL vs. 71% HAL). For RBL this pain was usually of low intensity (median VAS score on day 1: 3.0) and resolved rapidly to below baseline (median VAS score day on 7: 1.0). About 50% of patients required analgesics for the first few days after treatment. For HAL, the pain was significantly greater, with moderate pain at day 1 (median VAS score: 5.0) and mild pain on day 7 post procedure (median VAS score: 3.0). Pain had resolved in almost all patients by the 3-week assessment (median VAS score: RBL 0.0 vs. HAL 1.0). Analgesia was required by the majority after a HAL procedure on a daily basis for the first week but tailed off, such that at 3 weeks three-quarters of patients had stopped taking medication.

Combining and comparing results from published studies regarding pain following HAL is difficult, as measures of pain are, by definition, subjective, are often vague and vary significantly in both wording and outcome. Estimates of the incidence of pain, at least in the first postoperative day, vary from 15% to 18.5%.[5,19] No indication is given as to the degree of pain, presumably explaining the inconsistency with our results, for which significantly more patients experienced at least a degree of discomfort and only 6% had no pain at all. There are a few RCTs for which VAS scores are utilised in a similar fashion to our trial: collecting VAS scores on various days after the procedure. One RCT[24] comparing HAL with EH showed that for patients who were undergoing HAL, the mean scores were 5.5 on day 1, 2.5 on day 7, and 0 from day 14 onwards. Another RCT,[23] comparing HAL with SH, showed mean VAS scores of 3.1 on day 1, 1.6 on day 7, and 0.2 on day 21. A third trial,[30] comparing THD with SH, showed VAS scores of 2 on day 7, 1 on day 14, and 0.5 on day 21. All of these trials involved mucopexy. This may be the most painful part of the procedure. One trial that did not include mucopexy reported a mean VAS score of 5 on day 1, dropping to a mean of 3 by day 7.[32] Summarising these findings suggests most patients have moderate pain in the first few days after surgery, but that this pain recedes to minimal or no pain by 1–3 weeks. This is consistent with our results.

Anal pain is the most common complication after RBL. Mild pain is experienced by at least 25–50% of patients for the first 48 hours after banding,[15,70–74] which is also consistent with our results. The pain may be reduced by the concomitant use of local anaesthetic.[73] This was not routinely performed in our trial but may have significant clinical advantages as well as influencing the health-economic aspect of the treatment; about 25% of patients are reluctant to return to work, or to usual activities, on the day of the procedure[17,71,72] and 1% may be hospitalised due to the pain.[17]

Surgical complications

The incidences of SAEs from both interventions were low (12 in HAL group vs. 2 in RBL group). Two patients from the RBL group (2%) required hospitalisation (one for severe pain and one for bleeding). This is particularly relevant as the procedure is usually carried out in the outpatient department, often with minimal consent. A similar incidence of complications and hospitalisation has been highlighted elsewhere: one study[17] suggested immediate complications occurred in two-thirds of all patients. Most complications were related to pain, as in our trial, and 1% were hospitalised.

There is a vogue for some hospitals to arrange for the RBL procedure to be carried out in a day case theatre environment or during a separate, planned outpatient appointment, allowing for a formal consent process to take place. Day case admission may have avoided the need for hospitalisation in only one patient in our trial, who was complaining of immediate severe pain post procedure. At the very least, a formal consent process would have made clear to the patient the potential for these complications. However, there are significant cost implications.

Septic complications were seen in only one case in our series, but have been described extensively in the literature.[13,75] Sepsis may be local, such as perianal abscess formation, or even retroperitoneal sepsis[8,76–78] and Fournier's gangrene[79] described after RBL. Rarely the sepsis can be distant; pyogenic liver abscess formation[80–82] and endocarditis[83] have been described after RBL, whereas brain abscess has been described after HAL.[84] This reflects the transient bacteraemia that occurs in a small proportion of patients after haemorrhoidal procedures.[13] None of these rare complications was seen in our series and we do not recommend the routine use of antibiotic prophylaxis.

We saw significant bleeding (requiring admission with or without transfusion) in two patients (1.2%) after HAL and one patient (0.6%) after RBL. From the literature, bleeding occurs in around 4–5% of patients after a HAL procedure,[5,19] but only 0.15% of these were significant haemorrhages requiring blood transfusion.[5] The incidence of bleeding after RBL is 1–2.8%.[3,77] Significant bleeding requiring admission or intervention is more difficult to analyse, but pooling of the data available suggests an incidence of 0.7%.[3,11,14–18] Bleeding is more common if patients are taking anti-platelet agents, non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants.[3] These patients were excluded in our trial.

Urinary retention was seen in only two patients, both in the HAL group. Urinary retention has been described after both HAL and RBL, with a reported incidence of 0.7% after HAL[5] and about 0.3% after RBL.[3,11,14,15,17,18,83] Urinary retention is dependent on the severity of disease and degree of surgery, the analgesia requirement and pre-existing bladder outlet compromise.[85–87] In addition, day case treatment may reduce the incidence.[88] Both cases of urinary retention in our trial had HAL combined with significant mucopexy (more than five mucopexy sutures).

Other complications of HAL reported in the literature include thrombosis in 1.5–6.7%[5,19] and fissure in 0.8–10.3%.[5,19] Fissure was seen in 2% of our group. The incidence of thrombosis after RBL is < 1.5%[3,14] and fissure occurs in < 0.2%.[3,11,14,15,17,18,83] Vasovagal faints have been reported as a common occurrence after RBL (incidence 15%).[17] We saw one case each (0.5%) of perianal haematoma and vasovagal syncope, all in the RBL group; no fissures were reported following RBL. The low incidence of vasovagal syncope in our trial remains unexplained.

Clinical appearance of haemorrhoids at proctoscopy following recurrence

The data on clinical appearance at proctoscopy were limited, as most patients did not have re-examination. Those who were re-examined tended to be the patients who complained of persistent symptoms. Almost all of these patients had clinical assessment of unchanged or improved grade of haemorrhoids with only four (8%) from the RBL group being assessed as worse (increased prolapse, grade II–III piles).

Although increased swelling or haematoma as a result of the RBL intervention may explain the deterioration in this small group, this appears unlikely 6 weeks after the intervention. The time of day at which the assessment takes place may have an influence. Assessment later in the day may explain increased engorgement and therefore size. Another possibility is incorrect assessment at baseline. Grade II haemorrhoids are sometimes misclassified as grade III.[89]

Health-care costs and cost-effectiveness

The health-care cost analysis is striking. In the base-case results, HAL is around £1000 more expensive. As there is little difference in overall HRQoL between the two procedures, the ICER per additional QALY is very high and significantly exceeds the cost-effectiveness threshold of £20,000–30,000 per QALY. Even if a difference in recurrence is assumed (and this is not definite – see above), the cost per recurrence avoided is at least £5000. Essentially, HAL is highly unlikely to be cost-effective in terms of incremental cost per QALY.

Results of the subgroup analysis in patients with recurrence following RBL and new patients were broadly consistent with the overall population. The interaction effect of the grade of haemorrhoids resulted in an ICER of £108,478 per additional QALY for HAL conditional on patients with grade III piles.

In all scenarios of sensitivity analyses, the ICER remained > £100,000, indicating the robustness of our base-case results and suggesting that HAL is highly unlikely to be cost-effective. Extrapolating the CUA beyond the trial suggested a lower ICER of £21,887 per QALY, and HAL remained not cost-effective at £20,000 threshold. However, this estimate is highly uncertain because of the scarcity of good-quality evidence on long-term recurrence and utilities, particularly for HAL.

Additional data on health-care costs from other literature are sparse for this condition. Cost analysis has been carried out in one trial[51] comparing SH with RBL: the cost of RBL was estimated at £252, with the cost of SH being substantially higher and unlikely to be considered cost-effective at 1 year. However, the authors did assume that the cost of increased recurrence with RBL would mean that the difference in cost would fall over a longer time horizon. This may be true for HAL, although the relative low cost of RBL makes this unlikely. It is probably more cost-effective for patients to return for repeated RBL if recurrence occurs.

Another study[55] from the literature reported a trial-based CEA comparing SH with RBL for grade II symptomatic circumferential haemorrhoids, which is comparable with our study. The study[55] found that the mean cost for SH was £1483 higher than for RBL, and generated a negative difference in QALYs (–0.014), which was not statistically significant. Interestingly, this study[55] found that RBL is associated with higher recurrence rate than SH, with an estimated incremental cost of £4945 per recurrence avoided. The study[55] concluded that SH is highly unlikely to be cost-effective compared with RBL. This conclusion is broadly similar to our findings based on the HubBLe data and, therefore, HAL is also highly unlikely to be cost-effective compared with RBL.

Strengths and weaknesses

Generalisability

Among the strengths of this study was the pragmatic, multicentre design using a mix of NHS district general hospitals and teaching hospitals across the UK, which ensures that the results are generalisable to all patients seeking treatment for grade II/III haemorrhoids. The number of subjects recruited was such that there can be considerable confidence in the conclusions drawn from the data.

Definition of recurrence

The difficulties with definition of recurrence have already been highlighted earlier and clearly alluded to in the literature.[90] We feel that the significant lengths to which we have gone to carefully define recurrence should be regarded as a strength. Our data provide a clinically meaningful result of the true incidence of recurrence that is primarily patient reported, but has taken into account clinician-derived data of further consultations and procedures. Clinician reporting alone is likely to be misleading, but at the same time must be taken into account when it comes to differentiating the symptoms related to haemorrhoids and other conditions that may co-exist (skin tags, fissures, etc.) that may lead to a false diagnosis of recurrence.

Changes from baseline data

The original design of our trial incorporated a baseline assessment of symptoms at the date of randomisation. It became clear soon after the start of the trial that there was a discrepancy between the two arms of the trial, in that many patients randomised to the RBL group had their procedure almost immediately after randomisation whereas the HAL group often had to wait a significant period on a waiting list before surgery could be carried out. It is possible that symptomatology would have changed during that period. Certainly, deterioration could have occurred, but also improvement. Recognition of the disease issue and the impending thought of surgery may have resulted in an improved lifestyle, which, in turn, may have improved symptoms (see above). The issue of surgical waiting time delay has been noted before in surgical trials,[91] with a suggestion that the delay does not definitely alter data. To ensure that baseline data were collected consistently at a time close to intervention, we recollected the baseline data in those patients who were randomised to the HAL arm. Interestingly, although individual scores changed between randomisation and the actual procedure, the population average remained similar, suggesting that either could have been used as a plausible baseline value.

Justification of eligibility criteria

There are numerous therapies available for treatment of haemorrhoids, ranging from simple conservative therapies through to outpatient treatment and various surgical options. A consensus is emerging that a tailored approach is required for treatment of haemorrhoids based on grade.[92–94] Early-grade haemorrhoids can be effectively treated conservatively with diet,[95,96] alteration in lifestyle[94] and, perhaps, medical therapy,[38,97,98] whereas at the other end of the spectrum, grade IV circumferentially prolapsed piles may respond only to haemorrhoidectomy or SH. The eTHoS trial[99] hopes to provide data concerning the optimal procedure for the more advanced haemorrhoids.

Our main aim was to assess the effectiveness of HAL in the most clinically relevant scenario and compare with the most appropriate control. HAL appears to be most effective for treatment of grade II and early grade III piles[92] for which non-surgical treatment is also often utilised. These non-surgical methods include RBL, injection sclerotherapy, cryotherapy, infrared coagulation, laser therapy and diathermy coagulation. Of all of these non-surgical procedures, RBL seems to be the best in terms of compliance, long-term efficacy and side effects.[100] Therefore, participants with grade II or early grade III haemorrhoids were selected as investigation group and RBL was selected as our comparator.

The consensus concerning a tailored approach regarding the treatment of haemorrhoids is difficult to confirm from the evidence available, as most published meta-analyses involve standard pairwise trials comparing only two surgical treatments directly rather than all available treatments at once. A novel method of network analysis published by Simillis *et al.*[101] allows simultaneous comparison of all surgical treatments. It is unfortunate that this meta-analysis has focused on treatment of only grade III and IV haemorrhoids. The addition of data from the HubBLe trial to the existing data may allow a similar network meta-analysis for treatment of earlier-grade haemorrhoids.

Haemorrhoidal grading systems

We used the Goligher grading system for haemorrhoids,[102] as it is the most widely used grading system. This system has been criticised by many, particularly with regard to the definition of grade IV haemorrhoids. Goligher's original description of grade IV haemorrhoids[102] could include either skin tags or an external

haemorrhoid component alone or in addition to a mucosal prolapse that needs manual positioning. There is less ambiguity with regard to grade II haemorrhoids, and grade III haemorrhoids are patient reported (i.e. the need to manually reduce). However, we have to accept that the definition of early grade III haemorrhoids has an element of ambiguity. From a pragmatic point of view, the eligibility of a patient for the trial was decided by the surgeon, who had to decide if the grade III piles were potentially treatable by the interventions prescribed.

Learning curve

The HAL procedure appears simple and easy to learn, and most investigators have assumed this to be the case.[22,103,104] However, there are no good data on the learning curve and the steps that are required to achieve competence. The existence of a learning curve has been alluded to. Pucher et al.[19] pointed out that many case series include the particular centre's initial experience and describe a poorer outcome in the early patients.[66,105] Our trial required that surgeons had to have carried out at least five mentored cases and an additional five procedures prior to delivering the study intervention. This was based on manufacturers' recommendations, with no data to indicate that this was adequate to have reached the top of the learning curve for competence. HAL was performed by a clinician who was accredited for independent practice or supervised by a consultant in 94% of the cases in the trial, and all procedures were completed by clinicians who met the above criteria.

If we were to be more robust in our requirement for a satisfactory level of competence we would have had to assess reproducibility. Possible assessments could include placing the stitch adequately to achieve absence of the Doppler signal. However, Denoya et al.[25] describe the Doppler signal not changing in almost half of the vessels ligated in their study. Reproducibility could relate to detection of all branches of the superior haemorrhoidal artery. Ratto et al.[106] and Denoya et al.[25] identified at least six arteries in all patients. Six ligations were certainly not carried out in all of our participants. An interesting analysis would be to see if the number of ligations correlates with the incidence of recurrence.

To add to the difficulties in assessment of reproducibility that is dependent on efficacy of detection and effective ligation of all branches of the superior haemorrhoidal artery, recent scepticism has focused on the validity of de-arterialisation. Autopsy data indicate that additional branches of the superior rectal artery are not detected even with a Doppler probe.[107] Two RCTs[29,32] have randomised patients to HAL with or without Doppler probe guidance; both suggested similar results at 1-year follow-up.

Variation in intervention

Haemorrhoidal artery ligation

Haemorrhoidal artery ligation can be carried out using two equipment devices, both utilising the same principles. We allowed use of both devices within the trial, with sites invariably preferring the same device on all of their patients. There were no differences in outcomes between the different devices.

Our study included mucopexy as the standard of care. It is widely accepted that this part of the procedure produces more pain than simple artery ligation. A suture placed too near the dentate line or incorporating too much rectal tissue can result in increased pain and prolonged recovery. Again, there are few data in the literature to verify this finding, but some surgeons leave out this part of the procedure; others include it, as they claim it reduces the recurrence rate. However, data are lacking; only one previous study[30] has compared patients undergoing mucopexy to those with only artery ligation and showed no difference in end points but numbers were small. An interesting analysis would be to see if the number of mucopexy ligations correlates with the incidence of recurrence as well as the intensity of pain after surgery.

As alluded to in the learning curve discussion, some trials have suggested that the Doppler part of the procedure is unnecessary.[29,32] This conclusion remains controversial. One of the trials did not include mucopexy in either procedure arm and had short-term follow-up. Both had relatively low numbers of participants. Nevertheless, this may be a factor that could significantly reduce costs and should perhaps be a subject for future research.

Rubber band ligation

There are various potential variations in practice for the procedure of RBL. The procedure was originally described by Blaisdell[108] and modified by Baron using a forceps device.[109] More recently, and in the case of all of our recruiting centres, a suction device is used. Various suction banding devices can be used – some including a single firing, others delivering multiple bands. One small RCT[110] has suggested that suction banding is superior in terms of pain and bleeding.

Combination of RBL and injection sclerotherapy has been suggested as a more effective method of treatment than RBL alone,[111,112] but remains unproven in a well-designed trial.

The use of concomitant local anaesthetic has already been mentioned in the discussion about pain. Other variations in practice include the number of bands placed at each haemorrhoidal column. Again, no robust data exist to suggest that either technique is superior.

Variation between interventions

There was no blinding of participants or site staff in the trial as a result of the HAL procedure requiring general anaesthetic. Although equipoise was not measured in patients or clinicians, we believe equipoise was communicated to potential participants, as we produced a video for recruiting staff, highlighting the issues of randomisation and equipoise in relation to informed consent.

Symptom severity score

At the time of design of this trial, there were no validated scoring systems for haemorrhoids. The nearest we could come to such a system was that designed by Nyström *et al.*,[42] who altered a validated scoring system used for assessing colopouch function after rectal resection. The score has allowed a numerical assessment of the effect of both interventions, and results have complimented the dichotomous primary outcome. However, the score is not validated. For trials such as this, for which there is a poly-symptomatic condition and treatment effect must be guided by all of the patient's symptoms and their respective influence on QoL, there is a need for a validated score. Subsequent to our study starting, such a score, known as the Sodergren score, has been developed and validated using a small population of patients.[113] Further assessment of validity is required and data from our trial may allow further development in this area.

Length of follow-up

We chose '1 year' as the time for our primary outcome, as evidence suggests that most recurrences occur within the first year. However, there is definite evidence of continued recurrences with time for both procedures[3,27] and from our own data, with the striking deterioration seen at 1 year assessment compared with 6 weeks. For RBL, a further 20% may recur at 3 years, even if repeat RBL is carried out. The numbers may be similar for HAL.[37] The need for a longer-term follow-up for this subgroup is essential for further information regarding effectiveness and health economics. Modelling to assess ongoing costs and to see if HAL becomes cost-effective with time is planned but requires at least a further year of data to give more reliable predicted outcomes.

One other aspect related to follow-up is the issue of repeat banding. Our original protocol did not incorporate the analysis of HAL compared with repeat banding. The timing of this repeat banding was therefore not recorded. It is likely that most repeat procedures were carried out at, or soon after, the 6-week follow-up. However, a proportion of these were carried out later. For these patients the subsequent review at 1 year from the index procedure may not be long enough from the last banding episode to allow for confidence in the true level of recurrence.

Rubber band ligation as a course of therapy

In retrospect, an alternative design could have been considered in which HAL is compared with a 'course' of RBL. Such a course is difficult to define. Is it simply two episodes of RBL? Is it RBL, repeated only if there has been some response? Is it RBL ad infinitum? Is it RBL until the patient or clinician calls a halt and alternative procedures are requested? Design of such a trial is simple if the course is defined as two

episodes of RBL, perhaps 6 weeks apart, with follow-up for 1 year after the last RBL. Designing a trial to evaluate alternative treatment strategies is difficult. The current study has allowed the post hoc analysis of repeat RBL to be assessed while maintaining a feasible and pragmatic design.

Meaning of the study and implications for clinicians or policy-makers

Haemorrhoidal artery ligation is a more invasive procedure than RBL, requiring admission to hospital, longer waiting times, an anaesthetic and a more prolonged recovery. When offered an intervention for haemorrhoids, most patients would choose a more invasive procedure only if it were significantly more likely to achieve cure. Our data suggest that higher cure is true; the recurrence rate after HAL is significantly less than RBL and symptoms are more likely to be reduced. However, the recurrence rate for both procedures is high and may be considered by many patients as too high. Our data suggest that the HAL procedure in particular is not as effective as the current literature indicates. Similarly, recurrence after one episode of RBL is very likely. Many patients will undergo further interventions within the year and over one-quarter will still not consider themselves improved or cured. Given this level of recurrence, alternative procedures may be appropriate. However, a vigorous assessment of efficacy similar to this trial would be required in order to fairly compare these alternatives, be they conservative therapy or surgical intervention. The eTHoS trial[99] may provide this information for SH and haemorrhoidectomy.

Waiting times deserve an additional comment. It takes substantially longer for a HAL procedure to be carried out. Although not recorded, during the period of waiting for a HAL, patients will continue with symptoms whilst a large proportion of those in the RBL group would have had relief and improved QoL.

Despite this gloomy primary outcome data, it is important to state that symptom severity score, continence score and QoL improved after both interventions, suggesting that both interventions are beneficial to patients.

Would most patients who accept an intervention therefore choose HAL as it is the most effective procedure? The patient representative for the trial does not think that HAL appears to be the most effective procedure, and would opt for HAL only if it had much lower recurrence. Patients are likely to be influenced by other secondary factors, such as complications and QoL. Neither of these outcomes was different between interventions. Short-term pain was significantly higher in the HAL group, although the pain suffered after intervention tended to be mild to moderate and resolved within 1–3 weeks. Our trial also showed that many patients had to wait longer for a HAL, with most receiving RBL on the day of consult. Furthermore, of the screened patients who did not enter the trial, 128 opted for the RBL procedure and 70 for the HAL procedure. Given these factors, it could be argued that many patients would choose RBL, over HAL, as they would be inclined to 'take their chances' with a simple and quick outpatient procedure, without general anaesthetic, returning for a repeat procedure after a few months to years if recurrence occurred. A repeat RBL would be a simple and palatable option. Indeed many clinicians would consider RBL to consist of a 'course' of treatment rather than a single procedure, illustrated by the fact that it is common practice for many patients to be routinely followed up some weeks later, when repeat banding can easily be carried out. If those requiring repeat RBL to achieve control at 1 year are included as treatment successes then the difference between the two groups becomes insignificant.

Of course there is another factor that may influence the patient choice of HAL over RBL, and that is the long-term incidence of recurrence. Very few long-term data exist for RBL but the data that are available suggest a significant deterioration with time.[3] Some long-term trials on HAL also suggest significant attrition.[37] All trials on long-term data have significant methodological issues as well as significant ambiguity regarding the definition of recurrence. Our own data suggest significant deterioration in both groups over the year. It remains to be seen whether this attrition persists. HAL also appeared to improve symptoms more rapidly than RBL, although this is somewhat offset in practice by the aforementioned differential waiting time: RBL is a straightforward procedure that was usually done on the same day as randomisation, whereas the median waiting time for HAL was 60 days.

One further finding in our trial that has implications for both clinicians, and possibly commissioners, is the fact that two patients were hospitalised with complications after RBL. RBL is a procedure that is often carried out in the outpatient department at the time of initial consult: 20% of our recruiting centres follow this policy. Therefore, there is potentially no formal consent process and potentially inadequate immediate follow-up as the patient is usually discharged from the department. Some recruiting centres delay RBL, inviting the patient back to a formal day case theatre setting allowing for adequate informed consent and monitoring of potential complications. This would appear to be best practice, but does incur increased management costs.

Finally, it should be noted that there are massive cost implications for the HAL in these patients. RBL is relatively cheap, even if the patient returns to a day case setting for repeat banding.

Recommendations for future research

This trial adds to the growing body of evidence that proposes various surgical interventions for grade II and II haemorrhoids. Between them, the HubBLe and eTHoS trials include the four principle treatments that are used in this patient population: RBL, HAL, SH and EH. Pooling of these data sets with other data sets that are already available[101] may provide the opportunity to conduct an individual patient data (IPD) meta-analysis (network meta-analysis) to allow a comparison of all four interventions and will allow surgeons to tailor treatment options to the needs of individual patients. Considering the significant disease burden of haemorrhoids, this has the potential to provide powerful results. Further to this, a model-based economic evaluation should be conducted, synthesising all of the available evidence.

We have discussed the difficulties in defining recurrence in haemorrhoidal disease and the lack of a validated scoring system. The wealth of data available from this trial can now be analysed to enable such a system to be proposed and validated. This will provide future investigators with a robust and standardised tool with which to compare treatments and allow comparison between studies.

Our data have demonstrated that recurrence may increase with time. Further follow-up of the patient cohort would add to the results available regarding long-term effectiveness and allow an updated economic analysis. We feel that data collection at 2 and 3 years post intervention would provide clinically relevant information to aid surgeons and patients in treatment selection.

Other possible analyses of these data include correlation of the incidence of recurrence and the number of arterial branches ligated, as well as the number of mucopexy sutures. In addition, correlation with the degree of mucopexy and the intensity of pain would be helpful for clinical prediction of outcome.

Chapter 6 Conclusions

Haemorrhoidal artery ligation is a more clinically effective procedure than a single RBL intervention. However, if HAL is compared with repeat RBL then the procedures become equivalent in terms of recurrence. Similarly, symptom severity score, complications, QoL and continence score were no different between interventions, and patients had more pain in the early postoperative period after a HAL procedure. The HAL procedure is significantly more expensive than RBL and not cost-effective in terms of cost per QALY.

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All of the authors:

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- agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Publications

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Data sharing statement

Requests for patient-level data and statistical code should be made to the corresponding author and will be considered by the HubBLe trial management group who, although specific consent for data sharing was not obtained, will release data on a case-by-case basis following the principles for sharing patient-level data as described by Smith *et al.*[114] The presented data do not contain any direct identifiers; we will minimise indirect identifiers and remove free-text data to minimise the risk of identification.

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Appendix 1 Changes to protocol

Changes to protocol	Progress report	Date	Approved by
Protocol version 2.0: adverse events were clarified in the protocol and participant information sheet	1 (1 December 2012)	30 July 2012	NRES Committee Yorkshire & The Humber – South Yorkshire
Protocol version 3.0: clarified serious adverse event reporting to state that only related adverse events and serious adverse events will be reported	1 (1 December 2012)	30 August 2012	
Protocol version 4.0: a change was made to the eligibility criteria to exclude patients with hypercoagulability disorders (in addition to those on warfarin or clopidogrel)	1 (1 December 2012)	24 October 2012	
Protocol version 5.0: the baseline data collection was changed to the day of surgery, rather than at randomisation	2 (1 June 2013)	7 February 2013	
Protocol version 6.0: the inclusion criteria 'Either presenting for the first time or after one failure of RBL' was replaced by three exclusion criteria for clarification: *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; and patients that have had more than one RBL procedure in the past 3 years*	2 (1 June 2013)	25 March 2013	
Protocol version 7.0: the sentence 'patients will have at least 24 hours to decide whether to take part' was added to the protocol, to provide clarification	2 (1 June 2013)	30 April 2013	
Protocol version 8.0: a pre-randomisation questionnaire was added to the data collection schedule for participants	3 (1 December 2013)	5 July 2013	

NRES, National Research Ethics Service.

Appendix 2 Data collection tools

Screening assessment

HubBLe

Eligibility

Screening

Confidential

HubBLe

Screening eligibility

Date of screening [ ][ ] [ ][ ] [ ][ ][ ][ ]
d d m m y y y y

Gender ☐ Male ☐ Female   Age [ ][ ] years

Inclusion criteria

Adult age 18 years or over with symptomatic second or third degree haemorrhoids ☐ Yes ☐ No

Exclusion criteria

Patients that have had previous surgery for haemorrhoids	☐ Yes	☐ No
Patients that have had more than one RBL procedure in the past 3 years	☐ Yes	☐ No
Patients that have had more than one injection treatment in the past 3 years	☐ Yes	☐ No
Patient with known perianal sepsis, inflammatory bowel disease, colorectal malignancy or pre-existing sphincter injury	☐ Yes	☐ No
Patient with an immunodefiency	☐ Yes	☐ No
Patient unable to have general or spinal anaesthetic	☐ Yes	☐ No
Patient currently taking Warfarin or Clopidogrel, or have any other hypocoagulability condition	☐ Yes	☐ No
Patient currently taking Nicorandil	☐ Yes	☐ No
Patient is pregnant	☐ Yes	☐ No
Patient unable to give full informed consent	☐ Yes	☐ No
Patient previously randomised to this trial	☐ Yes	☐ No

Consent

Consent obtained? ☐ Yes ☐ No   Date of consent [ ][ ] [ ][ ] [ ][ ][ ][ ]
d d m m y y y y

Reason for non-consent

☐ Due to patient preference (i.e. They had a preferred procedure so didn't want randomisation)
→ ☐ HAL ☐ RBL ☐ Other [_____]
specify

☐ Unknown ☐ Other [_____]
specify

I certify that the data contained on this page are complete and accurate.
(To be signed and dated by the investigator or authorised member of the investigator's staff)

[_____] [_____] Date [ ][ ] [ ][ ] [ ][ ][ ][ ]
Signature *Print name* d d m m y y y y

Pre-randomisation questionnaire

HubBLe

Participant Questionnaire

Pre-Randomisation

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

The following questionnaire is broken down into four sections (Section A - Section E). Please work through all the sections as best you can from start to finish.

Each section asks you to indicate your answers to the questions by placing a tick (✓) in the appropriate box. Please read the questions carefully and answer each one as accurately as you can.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date of completion ☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

Section A: Describing your own health today (EQ-5D)

Your own health today

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today

A1 **Mobility**

- I have no problems in walking about ☐

- I have slight problems in walking about ☐

- I have moderate problems in walking about ☐

- I have severe problems in walking about ☐

- I am unable to walk about ☐

A2 **Self-care**

- I have no problems washing or dressing myself ☐

- I have slight problems washing or dressing myself ☐

- I have moderate problems washing or dressing myself ☐

- I have severe problems washing or dressing myself ☐

- I am unable to wash or dress myself ☐

A3 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐

- I have slight problems doing my usual activities ☐

- I have moderate problems doing my usual activities ☐

- I have severe problems doing my usual activities ☐

- I am unable to do my usual activities ☐

A4 **Pain/discomfort**

- I have no pain or discomfort ☐

- I have slight pain or discomfort ☐

- I have moderate pain or discomfort ☐

- I have severe pain or discomfort ☐

- I have extreme pain or discomfort ☐

A5 **Anxiety/Depression**

- I am not anxious or depressed ☐

- I am slightly anxious or depressed ☐

- I am moderately anxious or depressed ☐

- I am severely anxious or depressed ☐

- I am extremely anxious or depressed ☐

HubBLe

Section A: Describing your own health today (EQ-5D)

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine

100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

The worst health
you can imagine

HubBLe

Section B: Your level of pain

B1 **Please rate the level of pain related to your haemorrhoids that you are experiencing TODAY.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your pain today.

```
 0   1   2   3   4   5   6   7   8   9   10
No                                   Worst
pain                              imaginable
                                     pain
```

B2 During the last 7 days have you been taking any pain relief medication?   ☐ Yes ☐ No

B3 How many days, out of the last 7, have you taken any pain relief medication?   ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Section C: Assessment of faecal (stool) incontinence

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Rarely*	Sometimes*	Weekly*	Daily*
C1 Incontinence of solid stool	☐	☐	☐	☐	☐
C2 Incontinence of liquid stool	☐	☐	☐	☐	☐
C3 Incontinence of gas	☐	☐	☐	☐	☐
C4 Affects your lifestyle	☐	☐	☐	☐	☐

*Never = no episodes in the past four weeks; rarely = 1 episode in the past four weeks; sometimes = >1 episode in the past four weeks but <1 a week; weekly = 1 or more episodes a week but <1 a day; daily = 1 or more episodes a day.

C5 Are you able to delay defaecation ("hold on") for at least 15 minutes?   ☐ Yes   ☐ No

C6 Are you taking constipating medicines?   ☐ Yes   ☐ No

C7 Do you need to wear a pad or plug?   ☐ Yes   ☐ No

HubBLe

Section D: Haemorrhoids symptom score

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Sometimes*	Weekly*	Daily*
D1 How often do you experience pain from the haemorrhoids?	☐	☐	☐	☐
D2 How often do you experience itching or discomfort of the anus?	☐	☐	☐	☐
D3 How often do you experience bleeding when passing a motion?	☐	☐	☐	☐
D4 How often do you soil your underwear (mucous, liquid or solid discharge)?	☐	☐	☐	☐
D5 How often do you have to push back in a prolapsing haemorrhoid?	☐	☐	☐	☐

*Never = no episodes in the past four weeks; sometimes = >1 episode in the past four weeks but less than once per week; weekly = 1 - 6 times per week; daily = every day (1 or more episodes a day).

Section E: Height and Weight

E1 Weight ☐☐☐ . ☐ kg   OR   ☐☐ st ☐☐ lb

E2 Height ☐☐☐ . ☐ cm   OR   ☐ ft ☐☐ in

HubBLe

Thank you very much for being part of the HubBLe study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us to inform patients and doctors about haemorrhoid surgery in the future. It will be treated with the strictest confidence and kept securely.

Clinical assessment: baseline

HubBLe

Clinical Assessment

Baseline

Confidential

HubBLe

Date of assessment

☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

Patient details

Date of birth

☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

Ethnicity

White

☐ English / Welsh / Scottish /
Northern Irish / British

☐ Irish

☐ Gypsy or Irish Traveller

☐ Any other White background

☐ _____
specify

Asian / Asian British

☐ Indian

☐ Pakistani

☐ Bangladeshi

☐ Chinese

☐ Any other Asian background

_____
specify

☐ Prefer not to say

Mixed / multiple ethnic groups

☐ White and Black Caribbean

☐ White and Black African

☐ White and Asian

☐ Any other mixed / multiple ethnic background

_____
specify

Black / African / Caribbean / Black British

☐ African

☐ Caribbean

☐ Any other Black / African /
Caribbean background

_____
specify

Other ethnic group

☐ Arab

☐ Any other ethnic group

_____
specify

NHS number

☐☐☐ ☐☐☐ ☐☐☐☐

Consultant

_____

GP

_____

HubBLe

Smoking history

Smoking status

☐ Current smoker ☐ Previous smoker ☐ Never smoked

Number smoked per day ☐☐

Number of years smoked ☐☐

Medical history

Comorbidities

☐ Bleeding disorder

☐ Other haemorrhoid related

[_____]
specify

☐ Other relevant comorbidities

[_____]
specify

☐ None

Systemic medications related to increased risk of bleeding or reduced wound healing

☐ Aspirin

☐ Warfarin*

☐ Clopidogrel*

☐ Steroids

☐ Immunosuppressants*

☐ Nicorandil*

☐ Other

[_____]
specify

☐ None

*Please note that participants should not have been entered into the trial if they have an immunodeficiency or if they are currently taking Warfarin, Clopidogrel or Nicorandil. If they are, please complete a protocol non compliance form and send to the trial manager.

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Clinical data

Grade of haemorrhoids   ☐ II   ☐ III

Previous treatments for haemorrhoids*   ☐ Yes   ☐ No
                                                        ↓

Treatment / surgery	Number	Date of most recent (dd/mm/yyyy)
Banding* (Number of times not number of bands)	☐☐	☐☐ ☐☐ ☐☐☐☐
Injection sclerotherapy*	☐☐	☐☐ ☐☐ ☐☐☐☐
Open haemorrhoidectomy*	☐☐	☐☐ ☐☐ ☐☐☐☐
Stapled haemorrhoidopexy*	☐☐	☐☐ ☐☐ ☐☐☐☐
Other, specify _____	☐☐	☐☐ ☐☐ ☐☐☐☐

Weight   ☐☐☐.☐ kg

Height   ☐☐☐.☐ cm

---

*Please note that participants should not have been entered into the trial if they have had previous surgery for haemorrhoids, or if they have had more than one injection treatment or banding in the last three years.
If they have, please complete a protocol non compliance form and send to the trial manager.

Participant questionnaire: baseline

HubBLe

Participant Questionnaire

Baseline

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

The following questionnaire is broken down into four sections (Section A - Section D). Please work through all the sections as best you can from start to finish.

Each section asks you to indicate your answers to the questions by placing a tick (✓) in the appropriate box. Please read the questions carefully and answer each one as accurately as you can.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date of completion

d	d	m	m	y	y	y	y

HubBLe

Section A: Describing your own health today (EQ-5D)

Your own health today

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today

A1 **Mobility**

- I have no problems in walking about ☐

- I have slight problems in walking about ☐

- I have moderate problems in walking about ☐

- I have severe problems in walking about ☐

- I am unable to walk about ☐

A2 **Self-care**

- I have no problems washing or dressing myself ☐

- I have slight problems washing or dressing myself ☐

- I have moderate problems washing or dressing myself ☐

- I have severe problems washing or dressing myself ☐

- I am unable to wash or dress myself ☐

A3 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐

- I have slight problems doing my usual activities ☐

- I have moderate problems doing my usual activities ☐

- I have severe problems doing my usual activities ☐

- I am unable to do my usual activities ☐

A4 **Pain/discomfort**

- I have no pain or discomfort ☐

- I have slight pain or discomfort ☐

- I have moderate pain or discomfort ☐

- I have severe pain or discomfort ☐

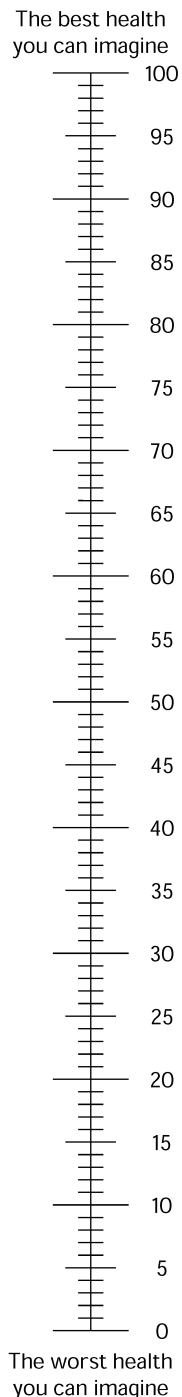- I have extreme pain or discomfort ☐

A5 **Anxiety/Depression**

- I am not anxious or depressed ☐

- I am slightly anxious or depressed ☐

- I am moderately anxious or depressed ☐

- I am severely anxious or depressed ☐

- I am extremely anxious or depressed ☐

HubBLe

Section A: Describing your own health today (EQ-5D)

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.
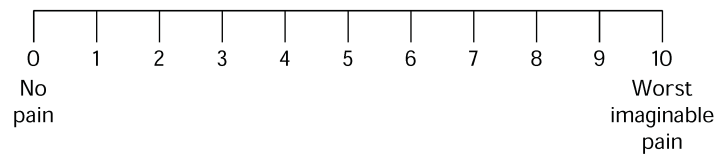
YOUR HEALTH TODAY =

The best health
you can imagine

| 100 |
| 95 |
| 90 |
| 85 |
| 80 |
| 75 |
| 70 |
| 65 |
| 60 |
| 55 |
| 50 |
| 45 |
| 40 |
| 35 |
| 30 |
| 25 |
| 20 |
| 15 |
| 10 |
| 5 |
| 0 |

The worst health
you can imagine

HubBLe

Section B: Your level of pain

B1 **Please rate the level of pain related to your haemorrhoids that you are experiencing TODAY.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your pain today.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

No pain   Worst imaginable pain

B2 During the last 7 days have you been taking any pain relief medication? ☐ Yes ☐ No

B3 How many days, out of the last 7, have you taken any pain relief medication? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Section C: Assessment of faecal (stool) incontinence

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Rarely*	Sometimes*	Weekly*	Daily*
C1 Incontinence of solid stool	☐	☐	☐	☐	☐
C2 Incontinence of liquid stool	☐	☐	☐	☐	☐
C3 Incontinence of gas	☐	☐	☐	☐	☐
C4 Affects your lifestyle	☐	☐	☐	☐	☐

*Never = no episodes in the past four weeks; rarely = 1 episode in the past four weeks; sometimes = >1 episode in the past four weeks but <1 a week; weekly = 1 or more episodes a week but <1 a day; daily = 1 or more episodes a day.

C5 Are you able to delay defaecation ("hold on") for at least 15 minutes? ☐ Yes ☐ No

C6 Are you taking constipating medicines? ☐ Yes ☐ No

C7 Do you need to wear a pad or plug? ☐ Yes ☐ No

HubBLe

Section D: Haemorrhoids symptom score

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Sometimes*	Weekly*	Daily*
D1 How often do you experience pain from the haemorrhoids?	☐	☐	☐	☐
D2 How often do you experience itching or discomfort of the anus?	☐	☐	☐	☐
D3 How often do you experience bleeding when passing a motion?	☐	☐	☐	☐
D4 How often do you soil your underwear (mucous, liquid or solid discharge)?	☐	☐	☐	☐
D5 How often do you have to push back in a prolapsing haemorrhoid?	☐	☐	☐	☐

*Never = no episodes in the past four weeks; sometimes = >1 episode in the past four weeks but less than once per week; weekly = 1 - 6 times per week; daily = every day (1 or more episodes a day).

Thank you very much for being part of the HubBLe study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us
to inform patients and doctors about haemorrhoid surgery in the future.
It will be treated with the strictest confidence and kept securely.

Procedure details

HubBLe

Procedure Details

Day 0

Confidential

HubBLe

Section A: Procedure details

Date of randomisation

d d m m y y y y

Treatment group

☐ RBL

☐ HAL

Date of procedure

d d m m y y y y

A1 Was antigcoagulation medication stopped before procedure?   ☐ Yes   ☐ No   ☐ N/A

A2 Date medication stopped

d d m m y y y y

A3 Grade of haemorrhoids   ☐ II   ☐ III

A4 Initials of surgeon performing procedure

A5 Grade of operating surgeon

☐ Consultant

☐ Staff or Associate Specialist

☐ Surgical Trainee

☐ Fellow

☐ Other

details

A6 Supervised by consultant   ☐ Yes   ☐ No   ☐ N/A

A7 Initials of supervising consultant

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Section B: Rubber Band Ligation

B1 **Positioning of bands**	**Number**		
☐ 3 o'clock	☐ 1	☐ 2	☐ >2
☐ 7 o'clock	☐ 1	☐ 2	☐ >2
☐ 11 o'clock	☐ 1	☐ 2	☐ >2
☐ Other	☐ 1	☐ 2	☐ >2

B2 Pain on application   ☐ Yes   ☐ No

details

B3 Procedural complications for RBL

☐ None

☐ Bleeding

details

☐ Haematoma

details

☐ Anaesthetic

details

☐ Other

details

HubBLe

Section B: Rubber Band Ligation

B4 **Post procedure complications for RBL**

☐ Bleeding

☐ Need for transfusion

☐ Urinary retention requiring catheterisation

☐ Severe pain

> *details*

☐ Other

> *details*

☐ None

B5 **Required admission?** ☐ Yes ☐ No

> *details*

B6 **Medications prescribed post procedure**

☐ Paracetamol

☐ Cocodamol

☐ Codeine

☐ NSAID

☐ Tramadol

☐ Laxative

☐ Antibiotic

☐ None

HubBLe

Section C: Haemorrhoidal Artery Ligation

Anaesthetic details

C1 **Anaesthetic**

☐ General and local

☐ Spinal

☐ Sedation only

C2 **Grade of anaesthetist:**

☐ Consultant

☐ Staff or Associate Specialist

☐ Surgical Trainee

☐ Fellow

☐ Other [   ]
    details

C3 **Supervised by consultant**   ☐ Yes   ☐ No   ☐ N/A

C4 **Initials of supervising consultant**   [   ]

Operative details

C5 **Make and model of kit**

[   ]

C6 Positioning of sutures	Pexy (✔)	Positioning of sutures	Pexy (✔)
☐ 1 o'clock	☐	☐ 7 o'clock	☐
☐ 2 o'clock	☐	☐ 8 o'clock	☐
☐ 3 o'clock	☐	☐ 9 o'clock	☐
☐ 4 o'clock	☐	☐ 10 o'clock	☐
☐ 5 o'clock	☐	☐ 11 o'clock	☐
☐ 6 o'clock	☐	☐ 12 o'clock	☐

HubBLe

Section C: Haemorrhoidal Artery Ligation

C8 Excision of skin tags ☐ Yes ☐ No ☐ N/A

C9 Intra-operative-complications

☐ None

☐ Bleeding

details

☐ Haematoma

details

☐ Anaesthetic

details

☐ Device Failure

details

☐ Other

details

Timings for surgery

C13 Entry into operating room ☐☐ : ☐☐ 24 hour format
h h m m

C14 Surgical start time ('knife to skin') ☐☐ : ☐☐ 24 hour format
h h m m

C15 Surgery stop time ☐☐ : ☐☐ 24 hour format
h h m m

C16 Time of leaving operating room ☐☐ : ☐☐ 24 hour format
h h m m

C11 Required admission? ☐ Yes ☐ No

details

HubBLe

Section C: Haemorrhoidal Artery Ligation

C10 Post-operative complications

☐ Bleeding

☐ Need for transfusion

☐ Urinary retention requiring catheterisation

☐ Severe pain

details

☐ Other

details

☐ None

C12 Medications on discharge

☐ Paracetamol

☐ Cocodamol

☐ Codeine

☐ NSAID

☐ Tramadol

☐ Laxative

☐ Antibiotic

☐ None

Discharge

C17 Date and time of discharge   ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐   ☐ ☐ : ☐ ☐   24 hour format
d   d   m   m   y   y   y   y   h   h   m   m

Participant questionnaire: 1 day

HubBLe

Participant Questionnaire

1 Day

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

The following questionnaire is broken down into two sections (Section A and Section B). Please work through all the sections as best you can from start to finish.

Each section asks you to indicate your answers to the questions by placing a tick (✓) in the appropriate box. Please read the questions carefully and answer each one as accurately as you can.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date of completion

d	d	m	m	y	y	y	y

HubBLe

Section A: Describing your own health today (EQ-5D)

Your own health today

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

A1 **Mobility**

- I have no problems in walking about ☐

- I have slight problems in walking about ☐

- I have moderate problems in walking about ☐

- I have severe problems in walking about ☐

- I am unable to walk about ☐

A2 **Self-care**

- I have no problems washing or dressing myself ☐

- I have slight problems washing or dressing myself ☐

- I have moderate problems washing or dressing myself ☐

- I have severe problems washing or dressing myself ☐

- I am unable to wash or dress myself ☐

A3 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐

- I have slight problems doing my usual activities ☐

- I have moderate problems doing my usual activities ☐

- I have severe problems doing my usual activities ☐

- I am unable to do my usual activities ☐

A4 **Pain/discomfort**

- I have no pain or discomfort ☐

- I have slight pain or discomfort ☐

- I have moderate pain or discomfort ☐

- I have severe pain or discomfort ☐

- I have extreme pain or discomfort ☐

A5 **Anxiety/Depression**

- I am not anxious or depressed ☐

- I am slightly anxious or depressed ☐

- I am moderately anxious or depressed ☐

- I am severely anxious or depressed ☐

- I am extremely anxious or depressed ☐

HubBLe

Section A: Describing your own health today (EQ-5D)

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine

100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

The worst health
you can imagine

HubBLe

Section B: Your level of pain

B1 **Please rate the level of pain related to your haemorrhoids that you are experiencing TODAY.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your pain today.

```
    0    1    2    3    4    5    6    7    8    9    10
   No                                            Worst
   pain                                       imaginable
                                                  pain
```

B3 During the last 24 hours have you been taking any pain relief medication?   ☐ Yes ☐ No

Thank you very much for being part of the HubBLe study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us
to inform patients and doctors about haemorrhoid surgery in the future.
It will be treated with the strictest confidence and kept securely.

Participant questionnaire: 7 days

HubBLe

Participant Questionnaire

| 7 Days |

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

The following questionnaire is broken down into two sections (Section A and Section B). Please work through all the sections as best you can from start to finish.

Each section asks you to indicate your answers to the questions by placing a tick (✓) in the appropriate box. Please read the questions carefully and answer each one as accurately as you can.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date of completion   ⬚ ⬚ ⬚ ⬚ ⬚ ⬚ ⬚ ⬚
                                 d   d   m   m   y   y   y   y

HubBLe

Section A: Describing your own health today (EQ-5D)

Your own health today

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

A1 **Mobility**

- I have no problems in walking about ☐

- I have slight problems in walking about ☐

- I have moderate problems in walking about ☐

- I have severe problems in walking about ☐

- I am unable to walk about ☐

A2 **Self-care**

- I have no problems washing or dressing myself ☐

- I have slight problems washing or dressing myself ☐

- I have moderate problems washing or dressing myself ☐

- I have severe problems washing or dressing myself ☐

- I am unable to wash or dress myself ☐

A3 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐

- I have slight problems doing my usual activities ☐

- I have moderate problems doing my usual activities ☐

- I have severe problems doing my usual activities ☐

- I am unable to do my usual activities ☐

A4 **Pain/discomfort**

- I have no pain or discomfort ☐

- I have slight pain or discomfort ☐

- I have moderate pain or discomfort ☐

- I have severe pain or discomfort ☐

- I have extreme pain or discomfort ☐

A5 **Anxiety/Depression**

- I am not anxious or depressed ☐

- I am slightly anxious or depressed ☐

- I am moderately anxious or depressed ☐

- I am severely anxious or depressed ☐

- I am extremely anxious or depressed ☐

Section A: Describing your own health today (EQ-5D)

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine

— 100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

The worst health
you can imagine

HubBLe

Section B: Your level of pain

B1 **Please rate the level of pain related to your haemorrhoids that you are experiencing TODAY.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your pain today.

```
    |   |   |   |   |   |   |   |   |   |   |
    0   1   2   3   4   5   6   7   8   9   10
   No                                      Worst
   pain                                    imaginable
                                           pain
```

B2 **Please rate the WORST level of pain that you have experienced SINCE YOUR OPERATION, approximately 7 days ago.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your worst pain since your operation.
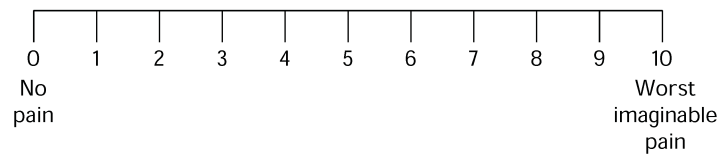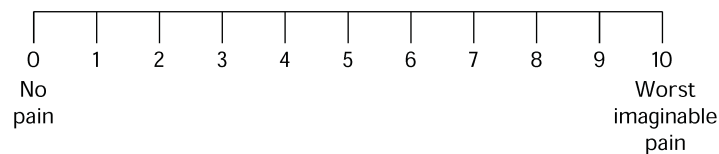
```
    |   |   |   |   |   |   |   |   |   |   |
    0   1   2   3   4   5   6   7   8   9   10
   No                                      Worst
   pain                                    imaginable
                                           pain
```

B3 During the last 7 days have you been taking any pain relief medication? ☐ Yes ☐ No

B4 How many days, out of the last 7, have you taken any pain relief medication? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Thank you very much for being part of the HubBLe study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us
to inform patients and doctors about haemorrhoid surgery in the future.
It will be treated with the strictest confidence and kept securely.

Participant questionnaire: 21 days

HubBLe

Participant Questionnaire

21 Days

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

The following questionnaire is broken down into two sections (Section A and Section B). Please work through all the sections as best you can from start to finish.

Each section asks you to indicate your answers to the questions by placing a tick (✓) in the appropriate box. Please read the questions carefully and answer each one as accurately as you can.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date of completion

d	d	m	m	y	y	y	y

Section A: Describing your own health today (EQ-5D)

| Your own health today |

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

A1 **Mobility**

- I have no problems in walking about ☐

- I have slight problems in walking about ☐

- I have moderate problems in walking about ☐

- I have severe problems in walking about ☐

- I am unable to walk about ☐

A2 **Self-care**

- I have no problems washing or dressing myself ☐

- I have slight problems washing or dressing myself ☐

- I have moderate problems washing or dressing myself ☐

- I have severe problems washing or dressing myself ☐

- I am unable to wash or dress myself ☐

A3 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐

- I have slight problems doing my usual activities ☐

- I have moderate problems doing my usual activities ☐

- I have severe problems doing my usual activities ☐

- I am unable to do my usual activities ☐

A4 **Pain/discomfort**

- I have no pain or discomfort ☐

- I have slight pain or discomfort ☐

- I have moderate pain or discomfort ☐

- I have severe pain or discomfort ☐

- I have extreme pain or discomfort ☐

A5 **Anxiety/Depression**

- I am not anxious or depressed ☐

- I am slightly anxious or depressed ☐

- I am moderately anxious or depressed ☐

- I am severely anxious or depressed ☐

- I am extremely anxious or depressed ☐

HubBLe

Section A: Describing your own health today (EQ-5D)

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100

- 100 means the best health you can imagine.
  0 means the worst health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine
— 100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health
you can imagine

HubBLe

Section B: Your level of pain

B1 **Please rate the level of pain related to your haemorrhoids that you are experiencing TODAY.**

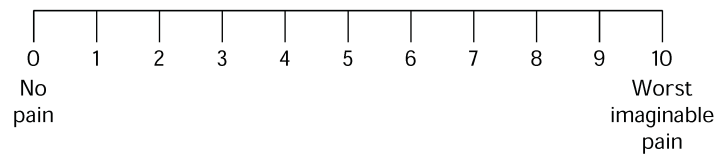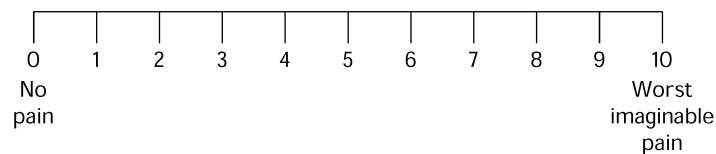The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your pain today.

```
    0   1   2   3   4   5   6   7   8   9   10
    No                                    Worst
    pain                              imaginable
                                           pain
```

B2 **Please rate the WORST level of pain that you have experienced in the last week.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your worst pain in the last week.

```
    0   1   2   3   4   5   6   7   8   9   10
    No                                    Worst
    pain                              imaginable
                                           pain
```

B3 During the last 7 days have you been taking any pain relief medication?   ☐ Yes ☐ No

B4 How many days, out of the last 7, have you taken any pain relief medication?   ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Thank you very much for being part of the HubBLe study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us
to inform patients and doctors about haemorrhoid surgery in the future.
It will be treated with the strictest confidence and kept securely.

Participant questionnaire: 6 weeks

HubBLe

Participant Questionnaire

6 Weeks

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

The following questionnaire is broken down into five sections (Section A - Section E). Please work through all the sections as best you can from start to finish.

Each section asks you to indicate your answers to the questions by placing a tick (✓) in the appropriate box. Please read the questions carefully and answer each one as accurately as you can.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date of completion

d	d	m	m	y	y	y	y

Section A: Describing your own health today (EQ-5D)

Your own health today

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today

A1 **Mobility**

- I have no problems in walking about ☐

- I have slight problems in walking about ☐

- I have moderate problems in walking about ☐

- I have severe problems in walking about ☐

- I am unable to walk about ☐

A2 **Self-care**

- I have no problems washing or dressing myself ☐

- I have slight problems washing or dressing myself ☐

- I have moderate problems washing or dressing myself ☐

- I have severe problems washing or dressing myself ☐

- I am unable to wash or dress myself ☐

A3 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐

- I have slight problems doing my usual activities ☐

- I have moderate problems doing my usual activities ☐

- I have severe problems doing my usual activities ☐

- I am unable to do my usual activities ☐

A4 **Pain/discomfort**

- I have no pain or discomfort ☐

- I have slight pain or discomfort ☐

- I have moderate pain or discomfort ☐

- I have severe pain or discomfort ☐

- I have extreme pain or discomfort ☐

A5 **Anxiety/Depression**

- I am not anxious or depressed ☐

- I am slightly anxious or depressed ☐

- I am moderately anxious or depressed ☐

- I am severely anxious or depressed ☐

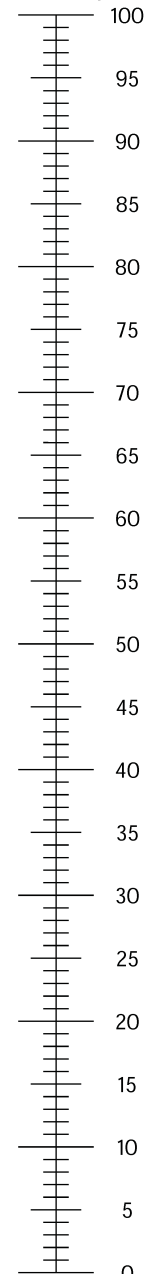- I am extremely anxious or depressed ☐

Section A: Describing your own health today (EQ-5D)

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

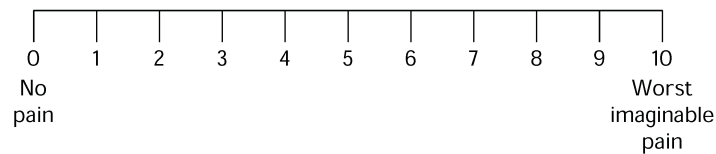The best health
you can imagine

100
95
90
85
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75
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45
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25
20
15
10
5
0

The worst health
you can imagine
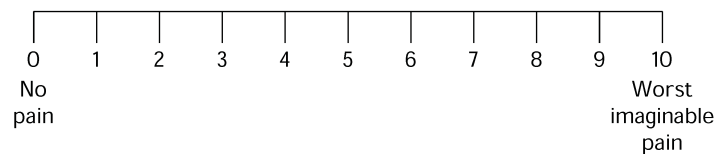
HubBLe

Section B: Your level of pain

B1 **Please rate the level of pain related to your haemorrhoids that you are experiencing TODAY.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your pain today.

```
 0   1   2   3   4   5   6   7   8   9   10
No                                      Worst
pain                                    imaginable
                                        pain
```

B2 **Please rate the WORST level of pain that you have experienced in the last week.**

The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain). Please draw a circle around the most appropriate number that describes your worst pain in the last week.

```
 0   1   2   3   4   5   6   7   8   9   10
No                                      Worst
pain                                    imaginable
                                        pain
```

B3 During the last 7 days have you been taking any pain relief medication?

☐ Yes ☐ No

B4 How many days, out of the last 7, have you taken any pain relief medication?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Section C: Assessment of faecal (stool) incontinence

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Rarely*	Sometimes*	Weekly*	Daily*
C1 Incontinence of solid stool	☐	☐	☐	☐	☐
C2 Incontinence of liquid stool	☐	☐	☐	☐	☐
C3 Incontinence of gas	☐	☐	☐	☐	☐
C4 Affects your lifestyle	☐	☐	☐	☐	☐

*Never = no episodes in the past four weeks; rarely = 1 episode in the past four weeks; sometimes = >1 episode in the past four weeks but <1 a week; weekly = 1 or more episodes a week but <1 a day; daily = 1 or more episodes a day.

C5 Are you able to delay defaecation ("hold on") for at least 15 minutes?   ☐ Yes   ☐ No

C6 Are you taking constipating medicines?   ☐ Yes   ☐ No

C7 Do you need to wear a pad or plug?   ☐ Yes   ☐ No

Section D: Haemorrhoids symptom score

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Sometimes*	Weekly*	Daily*
D1 How often do you experience pain from the haemorrhoids?	☐	☐	☐	☐
D2 How often do you experience itching or discomfort of the anus?	☐	☐	☐	☐
D3 How often do you experience bleeding when passing a motion?	☐	☐	☐	☐
D4 How often do you soil your underwear (mucous, liquid or solid discharge)?	☐	☐	☐	☐
D5 How often do you have to push back in a prolapsing haemorrhoid?	☐	☐	☐	☐

*Never = no episodes in the past four weeks; sometimes = >1 episode in the past four weeks but less than once per week; weekly = 1 - 6 times per week; daily = every day (1 or more episodes a day).

HubBLe

Section E: How are you keeping?

^{E1} Have you had any <u>emergency</u> admissions to hospital since your operation / procedure for haemorrhoids approximately 6 weeks ago? ☐ Yes ☐ No

^{E2} How many emergency admissions?
(if possible please provide details in the table below) ☐☐

Visit	Reason*	Day case or overnight stay?		Total nights admitted (if overnight stay)
1		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
2		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
3		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
4		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
5		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐

*e.g. Rubber Band Ligation (RBL); Haemorrhoidal Artery Ligation (HAL); Injection into piles; Operation;

^{E3} Have you had any <u>planned</u> (elective) haemorrhoid operations / procedures (e.g. haemorrhoidal artery ligation or rubber band ligation) since your operation / procedure for haemorrhoids approximately 6 weeks ago? ☐ Yes ☐ No

^{E4} How many new operations / procedures?
(if possible please provide details in the table below) ☐☐

Visit	Procedure*	Day case or overnight stay?		Total nights admitted (if overnight stay)
1		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
2		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
3		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
4		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
5		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐

*e.g. Rubber Band Ligation (RBL); Haemorrhoidal Artery Ligation (HAL); Injection; Traditional; Stapled; Operation

Section E: How are you keeping?

E5 Since your operation / procedure for haemorrhoids approximately 6 weeks ago, have you had any other non emergency visit to a hospital in relation to your haemorrhoids / haemorrhoid surgery (other than for a new operation / procedure)? ☐ Yes ☐ No

E6 How many times?
(if possible please provide details in the table below) ☐☐

Visit	Reason	Day case or overnight stay?		Total nights admitted (if overnight stay)
1		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
2		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
3		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
4		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
5		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐

E7 Have you seen your GP, in relation to your haemorrhoids, since your operation approximately 6 weeks ago? ☐ Yes ☐ No

E8 How many times? ☐☐

E9 Have you seen a nurse (at a GP practice), in relation to your haemorrhoids, since your operation approximately 6 weeks ago? ☐ Yes ☐ No

E10 How many times? ☐☐

Thank you very much for being part of the HubBLe study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us to inform patients and doctors about haemorrhoid surgery in the future. It will be treated with the strictest confidence and kept securely.

Clinical assessment: 6 weeks

HubBLe

Clinical Assessment

6 Week

Confidential

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HubBLe

Section A: Recurrence

Date of visit

| | | | | | | | |
|d|d|m|m|y|y|y|y|

A1 Prior to the 6 week visit has the patient needed to seek professional medical advice due to further symptoms from haemorrhoids since their procedure?   ☐ Yes ☐ No

A2 At the moment, are their symptoms from haemorrhoids:

☐ 1. Cured or improved compared with before starting treatment

☐ 2. Unchanged or worse compared with before starting treatment

Proctoscopy (if recurrence)

A3 Was a proctoscopy performed?   ☐ Yes ☐ No

A4 Haemorrhoidal tissue still present ☐ Yes ☐ No

A5 Grade

☐ I   ☐ II   ☐ III   ☐ IV

A6 Clinical findings

☐ Anal fistula

☐ Anal stenosis

☐ Residual anal skin tags

☐ Anal fissure

☐ Other _____

        specify

☐ None

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Section B: Interventions since discharge

B1 Not including the 6 week visit has the patient required an out-patient appointment since their RBL/HAL?   ☐ Yes ☐ No

B2 Did they require RBL?   ☐ Yes ☐ No

B3 Did they require another elective procedure?   ☐ Yes ☐ No

Please give details

B4 Has the patient been admitted to hospital with a complication since discharge?   ☐ Yes ☐ No

#	Reason*	Date of admission	Date of discharge
1		d d m m y y y y	d d m m y y y y
2		d d m m y y y y	d d m m y y y y
3		d d m m y y y y	d d m m y y y y
4		d d m m y y y y	d d m m y y y y
5		d d m m y y y y	d d m m y y y y

* e.g. Blood transfusion; Examination under anaesthetic; Excisional haemorrhoidectomy; Other, please give details

B5 Prior to the 6 week visit has the patient had any other elective / semi-elective procedures for haemorrhoids since their RBL/HAL?   ☐ Yes ☐ No

Please give details

Section C: Specific Complications

^{C1} Has the patient experienced any of the following complications since discharge? ☐ Yes ☐ No

☐ Urinary retention (which requires catheterisation)

☐ Pelvic sepsis

☐ Systemic complication related to haemorrhoids intervention(s)

☐ Other [   ]

specify

Section D: Unexpected SAEs

^{D1} Has the patient experienced any unexpected SAEs? ☐ Yes ☐ No

Please complete an SAE form.
Guidance is given in the 'Safety reporting guidance' document. Please contact the study team if you have any queries

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Section E: Need for further treatment

Medical treatment

E1 Is medical treatment required for persistent haemorrhoids or anal fissure?   ☐ Yes ☐ No

E2 Pharmaceutical treatment prescribed?   ☐ Yes ☐ No

☐ GTN Paste

☐ Diltiazem Paste

☐ Other, specify: _____

E3 Have you discharged the patient from clinical follow-up?   ☐ Yes ☐ No*

*If No, go to the next section

*Further planned treatment

E4 Is further surgical treatment required for persistent haemorrhoids?   ☐ Yes ☐ No

E5 Rubber band ligation   ☐ Yes ☐ No

E6 Stapled haemorrhoidopexy   ☐ Yes ☐ No

E7 Excisional haemorrhoidectomy   ☐ Yes ☐ No

E8 Surgery for complications   ☐ Yes ☐ No

Please give details _____

E9 Other colorectal surgery   ☐ Yes ☐ No

Please give details _____

Indication for surgery _____

Participant questionnaire: 1 year

HubBLe

Participant Questionnaire

1 Year

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

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Please start here:

Date of completion

d	d	m	m	y	y	y	y

HubBLe

Section A: Describing your own health today (EQ-5D)

Your own health today

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today

A1 **Mobility**

- I have no problems in walking about ☐

- I have slight problems in walking about ☐

- I have moderate problems in walking about ☐

- I have severe problems in walking about ☐

- I am unable to walk about ☐

A2 **Self-care**

- I have no problems washing or dressing myself ☐

- I have slight problems washing or dressing myself ☐

- I have moderate problems washing or dressing myself ☐

- I have severe problems washing or dressing myself ☐

- I am unable to wash or dress myself ☐

A3 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐

- I have slight problems doing my usual activities ☐

- I have moderate problems doing my usual activities ☐

- I have severe problems doing my usual activities ☐

- I am unable to do my usual activities ☐

A4 **Pain/discomfort**

- I have no pain or discomfort ☐

- I have slight pain or discomfort ☐

- I have moderate pain or discomfort ☐

- I have severe pain or discomfort ☐

- I have extreme pain or discomfort ☐

A5 **Anxiety/Depression**

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- I am slightly anxious or depressed ☐

- I am moderately anxious or depressed ☐

- I am severely anxious or depressed ☐

- I am extremely anxious or depressed ☐

HubBLe

Section A: Describing your own health today (EQ-5D)

- We would like to know how good or bad your health is TODAY.

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- 100 means the best health you can imagine.
  0 means the worst health you can imagine.

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100
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45
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30
25
20
15
10
5
0

The worst health
you can imagine

Section B: Assessment of faecal (stool) incontinence

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Rarely*	Sometimes*	Weekly*	Daily*
B1 Incontinence of solid stool	☐	☐	☐	☐	☐
B2 Incontinence of liquid stool	☐	☐	☐	☐	☐
B3 Incontinence of gas	☐	☐	☐	☐	☐
B4 Affects your lifestyle	☐	☐	☐	☐	☐

*Never = no episodes in the past four weeks; rarely = 1 episode in the past four weeks; sometimes = >1 episode in the past four weeks but <1 a week; weekly = 1 or more episodes a week but <1 a day; daily = 1 or more episodes a day.

B5 Are you able to delay defaecation ("hold on") for at least 15 minutes?　☐ Yes　☐ No

B6 Are you taking constipating medicines?　☐ Yes　☐ No

B7 Do you need to wear a pad or plug?　☐ Yes　☐ No

Section C: Haemorrhoids symptom score

Please tick the box which best describes your symptoms during the past four weeks:

	Never*	Sometimes*	Weekly*	Daily*
C1 How often do you experience pain from the haemorrhoids?	☐	☐	☐	☐
C2 How often do you experience itching or discomfort of the anus?	☐	☐	☐	☐
C3 How often do you experience bleeding when passing a motion?	☐	☐	☐	☐
C4 How often do you soil your underwear (mucous, liquid or solid discharge)?	☐	☐	☐	☐
C5 How often do you have to push back in a prolapsing haemorrhoid?	☐	☐	☐	☐

*Never = no episodes in the past four weeks; sometimes = >1 episode in the past four weeks but less than once per week; weekly = 1 - 6 times per week; daily = every day (1 or more episodes a day).

Section D: Recurrence

D1 Have you felt the need to seek professional medical advice due to further symptoms from haemorrhoids since your procedure?　☐ Yes　☐ No

D2 At the moment, do you feel your symptoms from your haemorrhoids are:

☐ 1. Cured or improved compared with before starting treatment

☐ 2. Unchanged or worse compared with before starting treatment

HubBLe

Section E: How are you keeping?

^{E1} Have you had any <u>emergency</u> admissions to hospital since your operation / procedure for haemorrhoids approximately one year ago?   ☐ Yes   ☐ No

^{E2} How many emergency admissions?
(if possible please provide details in the table below)   ☐☐

Visit	Reason*	Day case or overnight stay?		Total nights admitted (if overnight stay)
1		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
2		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
3		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
4		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
5		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐

* e.g. Rubber Band Ligation (RBL); Haemorrhoidal Artery Ligation (HAL); Injection into piles; Operation

^{E3} Have you had any <u>planned </u>(elective) haemorrhoid operations / procedures (e.g. haemorrhoidal artery ligation or rubber band ligation) since your operation / procedure for haemorrhoids approximately one year ago?   ☐ Yes   ☐ No

^{E4} How many new operations / procedures?
(if possible please provide details in the table below)   ☐☐

Visit	Procedure*	Day case or overnight stay?		Total nights admitted (if overnight stay)
1		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
2		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
3		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
4		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
5		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐

* e.g. Rubber Band Ligation (RBL); Haemorrhoidal Artery Ligation (HAL); Injection; Traditional; Stapled; Operation

HubBLe

Section E: How are you keeping?

E5 Since your operation / procedure for haemorrhoids one year ago, have you had any other non emergency visit to a hospital in relation to your haemorrhoids / haemorrhoid surgery (other than for a new operation / procedure)?   ☐ Yes ☐ No

E6 How many times?
(if possible please provide details in the table below)   ☐☐

Visit	Reason	Day case or overnight stay?		Total nights admitted (if overnight stay)
1		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
2		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
3		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
4		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐
5		☐ Day case (outpatients)	☐ Overnight stay (admitted)	☐☐

E7 Have you seen your GP, in relation to your haemorrhoids, since your operation approximately 1 year ago?   ☐ Yes ☐ No

E8 How many times?   ☐☐

E9 Have you seen a nurse (at a GP practice), in relation to your haemorrhoids, since your operation approximately 1 year ago?   ☐ Yes ☐ No

E10 How many times?   ☐☐

HubBLe

Thank you very much for being part of the HubBLe study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us
to inform patients and doctors about haemorrhoid surgery in the future.
It will be treated with the strictest confidence and kept securely.

Consultant questionnaire: 1 year

HubBLe

Consultant Questionnaire

1 Year

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

Date of completion

d   d   m   m   y   y   y   y

A1 Has the patient required any further non-emergency treatment for haemorrhoids ☐ Yes ☐ No
since the (RBL / HAL) 1 year ago?

A2 Which of the following?

Outpatient treatment:

☐ Rubber band ligation   number of times: ☐☐

☐ Injection sclerotherapy   number of times: ☐☐

Surgical treatment:

☐ Haemorrhoidal artery ligation   number of times: ☐☐

☐ Excisional haemorrhoidectomy   number of times: ☐☐

☐ Stapled haemorrhoidopexy   number of times: ☐☐

☐ Rubber band ligation (in theatre)   number of times: ☐☐

A3 Has the patient required emergency admission for symptoms related to their ☐ Yes ☐ No
haemorrhoids since their (RBL / HAL) 1 year ago?

A4 Did they have

☐ A blood transfusion

☐ An emergency operation / procedure

Details

A5 Has the patient visited you in relation to their haemorrhoids in the last year? ☐ Yes ☐ No

A6 How many times? ☐☐

A7 Has the patient visited another consultant or a GP practice in relation to their
haemorrhoids in the last year? ☐ Yes ☐ No

A8 How many times? ☐☐

GP questionnaire: 1 year

HubBLe

GP Questionnaire

1 Year

Confidential

Thank you for helping us with our research. We would be very grateful if you could complete this questionnaire.

HubBLe

GP Questionnaire

Date of completion

☐☐ ☐☐ ☐☐☐☐
d   d   m   m   y   y   y   y

A1 Has the patient required any further non-emergency treatment for haemorrhoids since the (RBL / HAL) 1 year ago? ☐ Yes ☐ No

A2 Which of the following?

Outpatient treatment:

☐ Rubber band ligation   number of times: ☐☐

☐ Injection sclerotherapy   number of times: ☐☐

Surgical treatment:

☐ Haemorrhoidal artery ligation   number of times: ☐☐

☐ Excisional haemorrhoidectomy   number of times: ☐☐

☐ Stapled haemorrhoidopexy   number of times: ☐☐

☐ Rubber band ligation (in theatre)   number of times: ☐☐

A3 Has the patient required emergency admission for symptoms related to their haemorrhoids since their (RBL / HAL) 1 year ago? ☐ Yes ☐ No

A4 Did they have

☐ A blood transfusion

☐ An emergency operation / procedure

Details ☐

A5 Has the patient visited you in relation to their haemorrhoids in the last year? ☐ Yes ☐ No

A6 How many times? ☐☐

A7 Has the patient visited another GP or the practice nurse in relation to their haemorrhoids in the last year? ☐ Yes ☐ No

A8 How many times? ☐☐

Serious adverse event form

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Serious Adverse Event Form

Randomisation No. | R ☐ ☐ / ☐ ☐ ☐ ☐

Participant Initials ☐ ☐

SAE details

Start date ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
　　　　　d　d　m　m　y　y　y　y

End date ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
　　　　　d　d　m　m　y　y　y　y

Procedure details

Treatment group　　☐ RBL

☐ HAL

Date of procedure ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
　　　　　　　　　　　d　d　m　m　y　y　y　y

Please choose and mark one of each below to rate the event:

Seriousness	**Frequency**	**Intensity**	**Outcome**
☐ Death*	☐ Isolated	☐ Mild	☐ Recovered
☐ Life threatening	☐ Intermittent	☐ Moderate	☐ Improved
☐ Inpatient hospitalisation**	☐ Continuous	☐ Severe	☐ Unchanged
☐ Prolongs hospitalisation	☐ Unknown		☐ Deterioration
☐ Persistent or significant disability/incapacity			☐ Persisted
☐ Congenital abnormality /birth defect			☐ Death*

*Date of death ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
　　　　　　　d　d　m　m　y　y　y　y

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Serious Adverse Event Form (cont.)

Randomisation No. R ☐ ☐ / ☐ ☐ ☐

Participant Initials ☐ ☐

**Hospital admission

Details

Start date ☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

Ongoing (✔) or End date
☐ ☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

Please also complete the 'Concomitant Medications' form if it's felt that the information could help in the clinical judgement of this SAE.

Date site staff became aware of the event ☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

Reporting person / position _____ / _____

Signature _____

Date of reporting ☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

To be completed by the PI / CI

Expected SAE? ☐ Yes ☐ No*   Relationship to RBL/HAL
- ☐ Definite*
- ☐ Probable*
- ☐ Possible*
- ☐ Unlikely
- ☐ Unrelated
- ☐ Not assessable

*In the event of a SUSAR please follow the expedited reporting procedure

Name of PI /CI _____

Signature _____

Date of signature ☐☐ ☐☐ ☐☐☐☐
d d m m y y y y

Study completion/discontinuation

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Study Completion / Discontinuation

Study completion

Has the participant completed the study (i.e. been contacted at 1 year regarding recurrence)?

☐ Yes   (please also complete the signature section at the bottom of the page)

☐ No   (please complete the sections below)

Discontinuation from procedure

Date of discontinuation   ☐☐ ☐☐ ☐☐☐☐
                                   d d   m m   y y y y

Reason for discontinuation of procedure

☐ Patient request

☐ Other _____
       specify

Has the participant agreed to continue in the study (despite not having study allocated procedure)?

☐ Yes   (please continue to complete the applicable forms, if at a later date the participant discontinues the study please complete the sections below. Once the final study visit has been completed please complete the signature section)

☐ No   (please complete the sections below)

Discontinuation from study

Date of last study contact   ☐☐ ☐☐ ☐☐☐☐
                                      d d   m m   y y y y

Reason for not continuing in the study

☐ Withdrew consent – date of withdrawal of consent   ☐☐ ☐☐ ☐☐☐☐
                                                         d d   m m   y y y y

☐ Participant died – date of death   ☐☐ ☐☐ ☐☐☐☐
                                            d d   m m   y y y y

☐ Participant lost to follow-up (and attempts to follow-up made in accordance with the protocol)

☐ Other _____
       specify

Signature

I certify that the data for this participant is complete and accurate.
(To be signed and dated by the investigator or authorised member of the investigator's staff)

Reporting person / position   _____ / _____

Signature   _____   Date signed   ☐☐ ☐☐ ☐☐☐☐
                                                                       d d   m m   y y y y

Appendix 3 Health-economic analyses: full regression results

Base–case analysis: seemingly unrelated regression: imputed data

Model Specification:
```
xi: mi estimate, cmdok: sureg (cost i.treat)(QALYs i.treat u_baseline)
```

Full regression results:
```
Multiple-imputation estimates                     Imputations     =         53
                                                  Number of obs   =        372
                                                  Average RVI     =     0.7246
                                                  Largest FMI     =     0.4113
DF adjustment:    Large sample                    DF:     min     =     313.07
                                                          avg     =     371.20
                                                          max     =     438.85
------------------------------------------------------------------------------
             |      Coef.    Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cost         |
   _Itreat_1 |   1026.946    124.4181    8.25    0.000      782.412    1271.479
       _cons |   723.1797    87.66625    8.25    0.000     550.8818    895.4776
-------------+----------------------------------------------------------------
QALYs        |
   _Itreat_1 |   .0098341    .0141964    0.69    0.489     -.018087    .0377552
  u_baseline |   .3306803     .053144    6.22    0.000     .2261226     .435238
       _cons |    .620022    .0492367   12.59    0.000     .5231453    .7168987
------------------------------------------------------------------------------
```

Subgroup analysis: recurrence following rubber band ligation

Model Specification:

```
xi: mi estimate, cmdok: sureg (cost i.treat)(QALYs i.treat u_baseline) if
rec_rbl==1
```

Full regression results:
```
Multiple-imputation estimates                     Imputations     =         53
                                                  Number of obs   =         77
                                                  Average RVI     =     0.5476
                                                  Largest FMI     =     0.3751
DF adjustment:    Large sample                    DF:     min     =     376.16
                                                          avg     =     478.60
                                                          max     =     529.11

------------------------------------------------------------------------------
             |      Coef.    Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cost         |
   _Itreat_1 |   1090.589     237.903    4.58    0.000     623.2357    1557.943
       _cons |   665.4697    157.6587    4.22    0.000     355.6765    975.2629
-------------+----------------------------------------------------------------
QALYs        |
   _Itreat_1 |   .0044161    .0270361    0.16    0.870    -.0487448    .0575769
  u_baseline |   .3230415    .1207478    2.68    0.008     .0858376    .5602455
       _cons |   .6282022    .1098891    5.72    0.000     .4122839    .8441206
------------------------------------------------------------------------------
```

Subgroup analysis: new patients

Model Specification:

```
xi: mi estimate, cmdok: sureg (cost i.treat)(QALYs i.treat u_baseline) if
rec_rbl==0
```

Full regression results:

```
Multiple-imputation estimates              Imputations    =         53
                                           Number of obs  =        295
                                           Average RVI    =     0.6379
                                           Largest FMI    =     0.4042
DF adjustment:   Large sample              DF:    min     =     324.14
                                                  avg     =     432.26
                                                  max     =     559.93


------------------------------------------------------------------------------
             |     Coef.    Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cost         |
   _Itreat_1 |  1007.901    141.7449     7.11   0.000     729.3875    1286.414
       _cons |  740.9366    100.0157     7.41   0.000     544.4848    937.3884
-------------+----------------------------------------------------------------
QALYs        |
   _Itreat_1 |  .0112024    .0158279     0.71   0.479    -.0199017    .0423064
  u_baseline |  .3329039    .0583516     5.71   0.000     .2181083    .4476996
       _cons |  .6175611    .0540217    11.43   0.000     .5112966    .7238256
------------------------------------------------------------------------------
```

Sensitivity analysis: using the NHS reference cost for the haemorrhoidal artery ligation procedure rather than the microcosting approach

Model Specification:

```
xi: mi estimate, cmdok: sureg (cost i.treat)(QALYs i.treat u_baseline)
```
Full regression results:

```
Multiple-imputation estimates              Imputations    =         53
                                           Number of obs  =        372
                                           Average RVI    =     0.7213
                                           Largest FMI    =     0.4138
DF adjustment:   Large sample              DF:    min     =     309.28
                                                  avg     =     334.93
                                                  max     =     373.45


------------------------------------------------------------------------------
             |     Coef.    Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cost         |
   _Itreat_1 |  1498.334    120.0387    12.48   0.000     1262.138     1734.53
       _cons |  622.6863    82.12316     7.58   0.000     461.2045    784.1681
-------------+----------------------------------------------------------------
QALYs        |
   _Itreat_1 |  .0098265    .0141951     0.69   0.489     -.018092     .037745
  u_baseline |  .3301776    .0530124     6.23   0.000     .2258849    .4344703
       _cons |  .6204764     .049095    12.64   0.000     .5238852    .7170676
------------------------------------------------------------------------------
```

Sensitivity analysis: controlling for the grade of haemorrhoids

Model Specification:
```
xi: mi estimate, cmdok: sureg (cost i.treat heam_grade)(QALYs i.treat u_baseline
heam_grade)
```

Full regression results:

```
Multiple-imputation estimates              Imputations    =          53
                                           Number of obs  =         372
                                           Average RVI    =      0.6956
                                           Largest FMI    =      0.4089
DF adjustment:   Large sample              DF:    min     =      316.70
                                                  avg     =      363.87
                                                  max     =      464.18


------------------------------------------------------------------------------
            |      Coef.    Std. Err.      t    P>|t|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
cost        |
  _Itreat_1 |   999.2027   121.8697     8.20   0.000     759.7181    1238.687
  heam_grade|    345.978   129.9347     2.66   0.008     90.41559    601.5405
      _cons |  -91.80375   317.6338    -0.29   0.773    -716.4896    532.8821
------------+-----------------------------------------------------------------
QALYs       |
  _Itreat_1 |   .0092111   .0142437     0.65   0.518    -.0188038    .0372259
  u_baseline|   .3306597   .0531358     6.22   0.000     .2261159    .4352036
  heam_grade|   .0078487   .0143074     0.55   0.584    -.0202813    .0359786
      _cons |   .6015382   .0594298    10.12   0.000     .4846319    .7184445
------------------------------------------------------------------------------
```

Sensitivity analysis: complete-case analysis

Model Specification:
```
sureg (cost i.treat)(QALYs i.treat u_baseline), corr
```

Full regression results:
```
Seemingly unrelated regression
------------------------------------------------------------------------------
Equation        Obs   Parms       RMSE    "R-sq"        chi2       P
------------------------------------------------------------------------------
cost            119       1    1037.993   0.2106       31.75   0.0000
QALYs           119       2    .0827048   0.6377      214.53   0.0000
------------------------------------------------------------------------------


------------------------------------------------------------------------------
            |      Coef.    Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
cost        |
      treat |
        HAL |   1073.279   190.4736     5.63   0.000     699.9581    1446.601
      _cons |   602.2028   137.4856     4.38   0.000      332.736    871.6696
------------+-----------------------------------------------------------------
QALYs       |
      treat |
        HAL |   .0103446   .0151768     0.68   0.495    -.0194014    .0400906
  u_baseline|   .7807911   .0533427    14.64   0.000     .6762414    .8853408
      _cons |   .2070643    .049401     4.19   0.000     .1102401    .3038885
------------------------------------------------------------------------------


Correlation matrix of residuals:

           cost    QALYs
  cost   1.0000
 QALYs   0.1063   1.0000

Breusch-Pagan test of independence: chi2(1) =      1.346, Pr = 0.2460
```

Sensitivity analysis: applying utility decrements for each subsequent procedure

Model Specification:
```
xi: mi estimate, cmdok: sureg (cost i.treat)(QALY2 i.treat u_baseline)
```

Full regression results:

```
Multiple-imputation estimates              Imputations    =         53
                                           Number of obs  =        372
                                           Average RVI    =     0.6984
                                           Largest FMI    =     0.4574
DF adjustment:   Large sample              DF:     min    =     253.21
                                                   avg    =     342.82
                                                   max    =     400.81


------------------------------------------------------------------------------
             |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cost         |
   _Itreat_1 |   1030.148   137.0264     7.52   0.000     760.2918    1300.005
       _cons |   727.0494   93.02419     7.82   0.000     544.0094    910.0894
-------------+----------------------------------------------------------------
QALY2        |
   _Itreat_1 |   .0082362   .0141725     0.58   0.562    -.0196371    .0361094
  u_baseline |    .330629   .0512231     6.45   0.000     .2299294    .4313285
       _cons |   .6200022   .0473644    13.09   0.000     .5268864    .7131181
------------------------------------------------------------------------------
```

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PHR

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