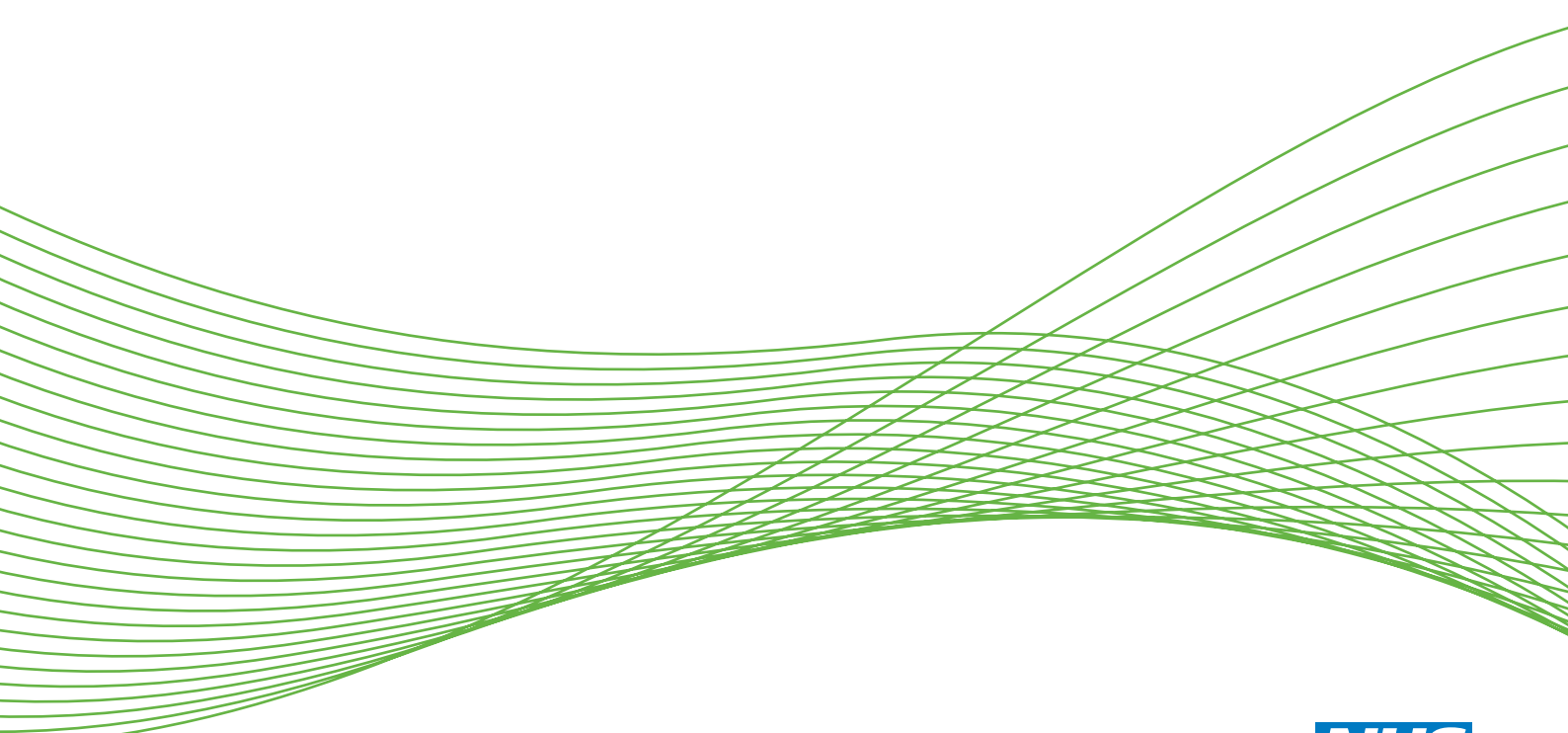




A pragmatic multicentre randomised controlled trial comparing stapled haemorrhoidopexy with traditional excisional surgery for haemorrhoidal disease: the eTHoS study

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***National Institute for
Health Research***

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Abstract

A pragmatic multicentre randomised controlled trial comparing stapled haemorrhoidopexy with traditional excisional surgery for haemorrhoidal disease: the eTHoS study

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Background: Haemorrhoids are a benign anorectal condition and are highly prevalent in the UK population. Treatments involve clinic-based procedures and surgery. The surgical procedures available include stapled haemorrhoidopexy (SH) and traditional haemorrhoidectomy (TH), and over 25,000 operations are performed for haemorrhoids annually in the UK. The disease is therefore important both to patients and to health service commissioners. Debate remains as to which of these surgical procedures is the most clinically effective and cost-effective.

Objective: The aim of this study was to compare the clinical effectiveness and cost-effectiveness of SH with that of TH.

Design: A large, open two-arm parallel-group pragmatic multicentre randomised controlled trial involving 32 UK hospitals and a within-trial cost-benefit analysis. A discrete choice experiment was conducted to estimate benefits (willingness to pay).

Participants: Patients with grades II–IV haemorrhoids who had not previously undergone SH or TH were included in the study.

Interventions: Participants were randomised to receive either SH or TH. Randomisation was minimised at 1 : 1, in accordance with baseline EuroQol-5 Dimensions, three-level version (EQ-5D-3L) score, haemorrhoid grade, sex and centre, via an automated system.

Main outcome measures: The primary outcome was area under the quality-of-life curve measured using the EQ-5D-3L descriptive system over 24 months, and the primary economic outcome was the incremental cost-effectiveness ratio. Secondary outcomes included disease-specific quality of life, recurrence, complications, further interventions and costs.

Results: Between January 2011 and August 2014, 777 patients were randomised (389 to receive SH and 388 to receive TH). There were 774 participants included in the analysis as a result of one post-randomisation exclusion in the SH arm and two in the TH arm. SH was less painful than TH in the short term. Surgical complications were similar in both arms. EQ-5D-3L score was higher for the SH arm in the first 6 weeks after surgery, but over 24 months the TH group had significantly better EQ-5D-3L scores (-0.073 , 95% confidence interval -0.140 to -0.006 ; $p = 0.0342$). Symptoms and further interventions were significantly fewer in the TH arm at 24 months. Continence was better in the TH arm and tenesmus occurred less frequently. The number of serious adverse events reported was 24 out of 337 (7.1%) for participants who received SH and 33 out of 352 (9.4%) for those who received TH. There were two deaths in the SH arm, both unrelated to the eTHoS (either Traditional Haemorrhoidectomy or Stapled haemorrhoidopexy for haemorrhoidal disease) study. Patient preference did not seem to influence the treatment difference. SH was dominated by TH as it cost more and was less effective. The net benefit for the TH arm was higher than that for the SH arm.

Limitations: Neither the participants nor the assessors were masked to treatment assignment and final recruitment was slightly short of the total target of 800. There were also substantial missing follow-up data.

Conclusions: While patients who received SH had less short-term pain, after 6 weeks, recurrence rates, symptoms, re-interventions and quality-of-life measures all favoured TH. In addition, TH is cheaper. As part of a tailored management plan for haemorrhoids, TH should be considered over SH as the surgical treatment of choice for haemorrhoids refractory to clinic-based interventions.

Future work: Perform an updated meta-analysis incorporating recently conducted European trials [eTHoS, HubBL (haemorrhoidal artery ligation versus rubber band ligation for the management of symptomatic second-degree and third-degree haemorrhoids) and LingaLongo (Cost-effectiveness of New Surgical Treatments for Haemorrhoidal Disease)].

Trial registration: Current Controlled Trials ISRCTN80061723.

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List of abbreviations

AUC	area under the curve	IQR	interquartile range
CEAC	cost-effectiveness acceptability curve	ISD	Information Services Division
CHaRT	Centre for Healthcare Randomised Trials	MD	mean difference
CI	confidence interval	MI	multiple imputation
CIS	Cleveland Incontinence Score	mWTP	marginal willingness to pay
CONSORT	Consolidated Standards of Reporting Trials	NICE	National Institute for Health and Care Excellence
CRF	case report form	NIHR	National Institute for Health Research
DCE	discrete choice experiment	OR	odds ratio
DMC	Data Monitoring Committee	PEDW	Patient Episode Database Wales
EQ-5D-3L	EuroQol-5 Dimensions, three-level version	PIL	patient information leaflet
eTHoS	either Traditional Haemorrhoidectomy or Stapled haemorrhoidopexy for haemorrhoidal disease	PMG	project management group
GP	general practitioner	QALY	quality-adjusted life-year
HAL	haemorrhoidal artery ligation	RBL	rubber band ligation
HES	Hospital Episode Statistics	RCT	randomised controlled trial
HSRU	Health Services Research Unit	REC	Research Ethics Committee
HSS	Haemorrhoid Symptom Score	SAE	serious adverse event
HTA	Health Technology Assessment	SD	standard deviation
HubBLE	haemorrhoidal artery ligation versus rubber band ligation for the management of symptomatic second-degree and third-degree haemorrhoids	SF-36	Short Form questionnaire-36 items
ICER	incremental cost-effectiveness ratio	SF-6D	Short Form questionnaire-6 Dimensions
INB	incremental net benefit	SH	stapled haemorrhoidopexy
IONTI	'to incentivise or not to incentivise'	SWAT	study within a trial
		TH	traditional haemorrhoidectomy
		TSC	Trial Steering Committee
		VAS	visual analogue scale
		WTP	willingness to pay

Plain English summary

Haemorrhoids (or 'piles') are swellings of blood vessels inside the anus. Common symptoms include bleeding, pain, itch and swelling. Haemorrhoids are graded in severity based on symptoms and size, from grade I (small piles with mild symptoms) to grade IV (large piles and major symptoms).

Traditional surgery for haemorrhoids, called traditional haemorrhoidectomy (TH), involves removal of haemorrhoids and is generally used for larger piles. Newer surgical techniques have been created as a result of an increased understanding of haemorrhoids; the treatment stapled haemorrhoidopexy (SH) was conceived over 15 years ago. Its potential advantages include less pain and a quicker return to normal activities. In this study, we wanted to compare SH with TH.

Patients could take part in the study if they had grades II–IV piles and had not had surgery before.

In this study we randomly allocated patients to receive either SH or TH. During the course of the study we asked participants about their quality of life, symptoms, recurrence of their piles and if they received further treatment. We compared the results of the different operational procedures. Within the first 6 weeks after surgery, participants who had received SH had a better quality of life because they had less pain, but over 24 months, the TH group had better quality of life, fewer symptoms and fewer further procedures.

Scientific summary

Background

Haemorrhoids are swellings in the veins underlying the lining of the bowel at the top of the anal canal. Symptoms from haemorrhoids include bleeding, pain, prolapse and perianal itch, all of which are common within the general population.

The initial management of haemorrhoids is community-based. Persistent symptoms merit referral for investigation and treatment. Outpatient treatment principally involves rubber band ligation (RBL) for lower-grade haemorrhoids, whereas surgical interventions are used for higher-grade haemorrhoids when banding has been unsuccessful. The Goligher system for grading haemorrhoids is used widely and was adopted for this study.

Given the prevalence of the condition, the management of haemorrhoidal disease continues to have considerable workload and cost implications for the NHS, with approximately 25,000 haemorrhoidal procedures being performed as hospital day-case or inpatient admissions in England over the period of 2006–7.

Over the last two decades (1997–2017), there has been an improved understanding of the anatomy of haemorrhoids, leading to the introduction of new surgical technologies into clinical practice. These technologies include stapled haemorrhoidopexy (SH) and haemorrhoidal artery ligation (HAL). The purported advantages of the new treatments, when compared with an existing surgical technique [excisional (or traditional) haemorrhoidectomy (TH)], were less postoperative pain and equal efficacy of symptom control.

Despite numerous small-scale randomised controlled trials (RCTs), significant doubts remain about the utility, efficiency and cost-effectiveness of SH and HAL. Evidence synthesised in systematic reviews and health technology assessments has highlighted the lack of good-quality data on which to base management choices.

Objectives

The aim of the eTHoS (either Traditional Haemorrhoidectomy or Stapled haemorrhoidopexy for haemorrhoidal disease) study was to answer the question ‘is SH more clinically effective and cost-effective than TH in the treatment of II–IV-grade haemorrhoids?’ The primary objective was to compare health-related quality of life between the two treatment arms derived over 24 months.

Methods

The eTHoS study was a large, multicentre UK pragmatic two-arm parallel-group RCT to establish whether or not SH surgical treatment improves clinical effectiveness and cost-effectiveness compared with TH. A discrete choice experiment (DCE) was conducted to estimate willingness to pay (WTP).

Study design and participants

Thirty-two UK NHS hospitals were involved in the study. Patients aged ≥ 18 years, with haemorrhoids of grades II–IV and from whom written informed consent could be obtained, were eligible to take part. Participants referred to hospital with haemorrhoids were included in the study if their symptoms did not resolve with RBL or HAL, or if their haemorrhoids were thought to be too large for these treatments to be successful. Patients who had received other haemorrhoid surgery were excluded.

Randomisation

Participants were randomised using minimisation to one of the two study groups on a 1 : 1 basis, using an automated system with telephone and web-based interfaces run from the study office.

Procedures

Participants were recruited by surgeons and research nurses in the outpatient department, who were also responsible for initiating randomisation. Study outcomes were collected at baseline, 1 week, 3 weeks, 6 weeks, 12 months and 24 months. Other data collected at baseline included, height, weight, grade of haemorrhoid, anticoagulant medication prescriptions, previous treatments for haemorrhoids and participant's treatment preference.

On the day of surgery, the grade of surgeon and anaesthetist was recorded, as well as the type of anaesthesia and the surgical technique performed. In addition, the length of time the procedure took and any intraoperative complications were recorded. Data on postoperative complications prior to discharge, which included postoperative bleeding, pelvic sepsis, the need for blood transfusion and urinary retention, were collected.

Follow-up consisted of a single clinical visit at the hospital and postal questionnaires over 24 months. At the 6-week clinic appointment, data on postoperative complications, including haemorrhage, requirement for blood transfusion, anal stenosis, anal fissure, urinary retention (which required catheterisation), residual anal skin tags, difficult defaecation, wound discharge, pelvic sepsis and pruritus, were collected. Further haemorrhoid-related interventions since discharge were recorded, as well as the need for further planned medical or surgical interventions for haemorrhoids or complications associated with treatment.

EuroQol-5 Dimensions, three-level version (EQ-5D-3L) and visual analogue scale (VAS) pain data were collected by postal questionnaire at 1 and 3 weeks following surgery. The EQ-5D-3L and the Short Form questionnaire-36 items (SF-36), Haemorrhoid Symptom Score (HSS), Cleveland Incontinence Score (CIS) and VAS data were collected by postal questionnaire at 6 weeks following surgery. In addition, questionnaires distributed at 12 and 24 months after randomisation also collected data on patient-reported haemorrhoid recurrence and further operations. The main outcome assessment was planned at the 24-month (from the date of randomisation) follow-up.

Consent was sought from all participants to be flagged for notification of haemorrhoidal recurrence and, to evaluate long-term safety, the participants were investigated for further haemorrhoidal surgery through Hospital Episode Statistics (HES) in England, the Patient Episode Database Wales (PEDW) in Wales and Information Services Division (ISD) data in Scotland, when all participants had reached 12 months post randomisation.

Outcomes

The primary outcome was the area under the curve (AUC) over 24 months measured by the EQ-5D-3L at baseline, 1 week, 3 weeks, 6 weeks (post operative), 12 months and 24 months (post randomisation). The AUC is expressed in years and can be interpreted as quality-adjusted life-years (QALYs).

Patient-reported secondary outcomes were generic health profile as measured by the SF-36 and the EQ-5D-3L, VAS pain score, CIS, HSS, postoperative analgesia consumption, recurrence of haemorrhoids and tenesmus. The clinical secondary outcomes were further interventions, intra- and postoperative complications, including haemorrhage, requirement for blood transfusion, anal stenosis, anal fissure, urinary retention (which required catheterisation), residual anal skin tags, difficult defaecation, wound discharge, pelvic sepsis and pruritus. The primary study economic outcome was incremental cost per QALYs gained with QALYs based on the responses to the EQ-5D-3L over 24 months.

Results

In total, 1127 patients were screened between January 2011 and August 2014, with 777 randomised to receive either SH or TH (389 to SH and 388 to TH). There were 774 participants included in the analysis as a result of one postrandomisation exclusion in the SH arm and two in the TH arm. There were 721 participants who received surgery; of these, 37 participants randomised to SH received TH and 29 randomised to TH received SH. The remainder of participants (18 in the SH arm and 11 in the TH arm) received a non-randomised intervention, and two in the SH arm were unknown. The duration of the operation (0.4 hours) and length of hospital stay (0.4 days) was the same in each group and the median time of follow-up was 731 days [interquartile range (IQR) 377–736 days] for the SH arm and 731 days (IQR 514–738 days) for the TH arm.

The primary outcome, EQ-5D-3L AUC over 24 months, favoured TH [−0.073, 95% confidence interval (CI) −0.140 to −0.006; $p = 0.034$]. The secondary analysis over 24 months post randomisation showed no evidence of a difference between treatment arms, but favoured SH over 6 weeks post surgery. For the secondary outcomes, both the physical and mental component scores (SF-36) at 12 months post randomisation showed evidence of a difference in favour of TH [physical summary: −1.79, 95% CI −3.06 to −0.51, $p = 0.006$; and mental summary: −1.71, 95% CI −3.34 to −0.08, $p = 0.040$]. At 12 months post randomisation, more participants reported that their haemorrhoids had come back in the SH arm ($n = 94$, 31.9%) than in the TH arm (39, 14.0%) (odds ratio 2.96 95% CI 2.02 to 4.32; $p < 0.001$). This also occurred at 24 months, with more participants reporting reoccurrence in the SH arm ($n = 134$, 42.3%) than in the TH arm ($n = 76$, 25.3%). There was no clear sign of a participant treatment-preference effect.

The number of serious adverse events (SAEs) reported was 24 out of 337 (7.1%) for participants who received SH and 33 out of 352 (9.4%) for those who received TH. There were two deaths in the SH arm, both unrelated to the eTHoS study.

The mean cost per patient for SH was £941 [standard deviation (SD) £415], and £602 (SD £507) for TH. The adjusted analysis mean difference in total costs was £337 (95% CI £251 to £423) higher for SH than for TH. The QALY results for SH were 1.62 (0.43), and 1.69 (0.38) for TH. The adjusted analysis mean difference in QALYs was −0.070 (95% CI −0.127 to −0.011). Therefore, on average, SH costs were higher than those for TH, and SH had lower QALYs than TH, so it was dominated by TH. The cost–utility analysis indicated that SH had zero probability of being cost-effective at both £20,000 and £30,000 thresholds. The DCE results indicated that WTP was highest for TH, but the values were not statistically significantly different. Although total WTP estimates were positive for both treatments (£1277 for SH and £1367 for TH), the net benefit was higher for TH than that for SH (£765 vs. £330).

Conclusions

The eTHoS study showed better generic quality-of-life scores over the 24-month follow-up period for TH over SH. Short-term post-surgery quality-of-life scores favoured SH, reflecting the lower rates of pain in the immediate postoperative period. SH was less painful, but this difference disappeared by 6 weeks. At 12 months, the EQ-5D-3L quality-of-life scores were similar; however, the physical and mental health domains of the SF-36 favoured TH. At 24 months the primary outcome favoured TH. In addition, there were also fewer residual haemorrhoid symptoms, recurrences and re-interventions.

Both treatments showed similar operating times, length of stay and return to normal activity at 6 weeks. This refutes the common argument that a shorter operating time and length of stay after SH offsets the cost of a stapler.

Clinical recurrence of haemorrhoids was measured using the HSS, a patient-reported dichotomous outcome measure, and recurrence data were collected from national registry databases (HES, ISD and PEDW). We chose to assess recurrence over 24 months, expecting to capture a proportion of patients who report symptom relapse after 12 months.

Continence was an important outcome measure for this study. As expected, in the immediate postoperative period, the scores were relatively impaired when compared to the baseline. Thereafter, continence scores were significantly better in the TH arm up to 24 months after randomisation.

The economic analysis convincingly demonstrated that TH dominates SH, as it costs £337 less than SH and is 0.07 QALYs more clinically effective than SH. SH has a < 1% probability of being considered cost-effective at the £30,000 threshold. The results of the economic analysis differ from work previously published that reported that TH and SH had similar costs and QALYs, but the costs of a staple gun were offset by savings in length of hospital stay. In our study, the length of inpatient stay was similar across both groups, so there were no cost-savings in that area, and our QALY results, based on a 2-year follow-up period, indicated that SH had fewer QALYs than TH.

The main limitations of this study are twofold; final recruitment to eTHoS was just short (97%) of the target number and, furthermore, there were substantial and greater than expected missing data at the 24-month follow-up, despite multiple strategies to mitigate this. This perhaps reflected the population (working age), the condition (chronic and considered by some to be a sensitive subject) and the nature of the follow-up. Nevertheless, the study still had sufficient statistical precision to detect differences between treatment groups. There was also a noticeable level of non-compliance with allocation (some not receiving surgery, and some receiving a different operation), reflecting, perhaps, a mixture of clinical reality and some surgeon and patient preferences regarding treatment. Such non-compliance tends to dilute a genuine effect. Despite this, the primary analysis still supported a difference in favour of TH, and the per-protocol analysis of only those who complied with allocation was consistent with this finding. Participant treatment preferences also did not seem to affect the findings. More generally, it is worth noting that the delivery of the interventions reflected routine clinical practice across a range of centres in terms of the surgeons participating (their experience) and how the interventions were delivered (specific technique and centre practices). Taken together, we believe the findings are robust and generalisable.

Despite some published postoperative complications having been severe, particularly with regard to pelvic sepsis, rectal perforation and rectovaginal fistula formation, in the introduction of a new surgical treatment there were no reports of these complications within this study. SAEs were equally distributed through both arms of the eTHoS study. All the events were expected and largely consisted of pain, bleeding, constipation and urinary retention.

This study is among the largest RCTs for haemorrhoids ever carried out. No prescriptive entry criteria were set for hospital inclusion and we are therefore confident that the results are generalisable. A 24-month follow-up period was used to capture symptom recurrence and further interventions; therefore, a median follow-up of 731 days is a further strength of this study. A pragmatic approach to surgeon's credentials was adopted. At the inception of the study, both SH and traditional excisional surgery were established in common surgical practice and surgeons were required to have undergone appropriate recognised training for both procedures. The effect of surgical experience on outcomes can partially be mitigated by the high level of consultant involvement in performing the surgery (71.5% in the SH arm and 62.0% in the TH arm) and the low incidence of adverse events.

Traditional haemorrhoidectomy is both more clinically effective and less costly than SH; it is more painful in the short term. Return to normal activity rates were equal. In addition to superior quality-of-life measures, HSS, continence and tenesmus rates and the need for further surgery were all lower in TH. TH is, therefore, a superior surgical treatment for the management of grades II–IV haemorrhoids than SH.

Future work should include an updated network meta-analysis that encompasses the results from this trial and other large contemporary trials on haemorrhoids.

Trial registration

This trial is registered as ISRCTN80061723.

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Chapter 1 Introduction

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The eTHoS study: either Traditional Haemorrhoidectomy or Stapled haemorrhoidopexy for haemorrhoidal disease

In 2010, the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme funded the eTHoS (either Traditional Haemorrhoidectomy or Stapled haemorrhoidopexy for haemorrhoidal disease) study. The study evolved in response to a HTA programme-commissioned call issued in 2008 inviting proposals for a study. The call itself arose after completion of a HTA-commissioned and -funded evidence synthesis written by Burch *et al.*² One of the key recommendations was the need for a well-designed, multicentre, prospective randomised controlled trial (RCT) to inform the evidence for the management of haemorrhoidal disease. This report describes the research.

The eTHoS study was a major multicentre UK-based RCT investigating the clinical effectiveness (including safety) and cost-effectiveness of stapled haemorrhoidopexy (SH) and traditional excisional haemorrhoidectomy (TH) for adult patients with grade II, III or IV haemorrhoids.

This chapter reflects clinical practice, particularly within the NHS, and the evidence available at the time of study inception, and discusses changes in NHS practice and any relevant literature published since 2009.

Background

The burden of the problem

Haemorrhoidal disease is common in all age groups from the mid-teens onwards; however, the direct causes are unclear. Haemorrhoids, or 'piles' as they are most commonly known, are defined as enlarged areas of vascular tissue at the top of the anal canal. Symptoms from haemorrhoids include bleeding, pain, itch and prolapse, and these can have an impact on a person's quality of life. For significantly enlarged and protruding haemorrhoids, surgery is often advised as an effective way to control the symptoms.³

The most commonly used clinical grading system for haemorrhoids is the one created by Goligher,⁴ who described four stages of haemorrhoids: grade I – protrusion of piles into anal canal; grade II – prolapse of haemorrhoids externally on defaecation, but return into the anal canal spontaneously; grade III – prolapse of haemorrhoids on defaecation and remain prolapsed until they are manually replaced into the anus; and grade IV – prolapsed and irreducible haemorrhoids.

The treatment of patients with haemorrhoidal disease continues to have considerable workload and cost implications for the NHS. Approximately 25,000 haemorrhoidal procedures were performed as hospital day-case or inpatient admissions in England over the period of 2006–7.⁵ The treatment of haemorrhoidal disease is directed at relieving its related symptoms and this remains the current surgical philosophy.

Management of disease

The management of haemorrhoids is initially community-based. For early-grade haemorrhoids (grades I and II) patients are advised to avoid straining at stool and asked to increase the proportion of fruit and fibre in their

diets. There is a large range of proprietary treatments that are available 'over the counter'. These include topical creams and suppositories. Their efficacy is poor. Patients with refractory symptoms, or who have symptoms that cross over with those of bowel cancer and inflammatory bowel disease, are referred to a surgical outpatient clinic for investigation and treatment. Once inflammatory bowel disease and cancer have been excluded, the first line of treatment for grades II–III haemorrhoids is rubber band ligation (RBL). RBL is often offered as a 'course' of repeated treatments in the outpatient setting. RBL is successful in treating symptoms around 40% of the time and those patients who remain symptomatic after treatment are offered surgery. There are three main surgical techniques for haemorrhoids. These include excisional (or traditional) haemorrhoidectomy, SH and haemorrhoidal artery ligation (HAL).

In 2009, there were two main standard surgical treatments for haemorrhoids: traditional (or excisional) surgery and SH. A third operation, HAL, had been introduced but was not then in widespread use.

Traditional surgical haemorrhoidectomy

Traditional haemorrhoidectomy involves excision of the haemorrhoidal cushions and has generally been advocated for larger symptomatic haemorrhoids (grades III and IV). The technique involves the excision of haemorrhoid tissue. This is most commonly done by electrocautery, but occasionally sharp dissection with scissors is used. Other energy devices, the Harmonic® scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA) and the LigaSure™ device (Valleylab, Boulder, CO, USA) can also be used. The resulting wounds can either be sewn up (closed haemorrhoidectomy or Ferguson technique) or left open (open haemorrhoidectomy or Milligan–Morgan technique). This traditional approach, while effective, is nonetheless associated with severe immediate postoperative pain. Improved understanding of the pathogenesis of haemorrhoids⁶ and of the complications associated with excisional haemorrhoidectomy led to the invention of newer surgical procedures, including SH.

Stapled haemorrhoidopexy

Stapled haemorrhoidopexy was first developed by Longo at the end of the last millennium.⁷ Its potential advantages over traditional surgery included a reduction of operating time, length of hospital stay, time to return to work and postoperative pain.⁸ These features, compared with traditional haemorrhoid surgery, made SH attractive to patients and health-care providers at the time. However, uncertainties remained concerning complication rates, recurrence of symptoms and costs, which impeded its extensive use in the NHS. The stapling devices used for the procedure have evolved over the last two decades (1997–2017). The design has been refined to reduce the chance of postoperative bleeding and for the gun to be more effectively used in male patients (who have a narrower pelvis). Other manufacturers have also entered the market and produced guns that are significantly cheaper (Chex CPH 32 staple gun; Frankenman, Sheung Wan, Hong Kong) than the leading product, the PPH03 staple gun (Johnson & Johnson, New Brunswick, NJ, USA).

A newer technique, HAL was beginning to be adopted but was not being used across the NHS to any great degree. This surgical technique is also performed under general anaesthetic and involves the identification and ligation of the haemorrhoid arteries that feed haemorrhoids. The procedure is often combined with a suture that 'pexies' the prolapsing tissue back into the upper anal canal.

Evidence leading to the inception of the eTHoS study

Multiple RCTs comparing SH with TH and/or other conventional surgeries were analysed in four systematic reviews and a HTA journal publication.^{2,9–12} The HTA publication included a review of the clinical effectiveness data from 27 RCTs ($n = 2279$). When comparing SH with TH, the studies showed equivalent complication and pain rates at day 21 post surgery. However, SH patients had less pain in the immediate postoperative period (first week) than those who received TH. Over the longer term, there was a significantly increased rate of residual prolapse requiring re-intervention with SH; however, there was no evidence of a difference in the number of patients experiencing pain or bleeding between the SH arm and the TH arm. The economic evaluations of the two interventions found that TH dominated SH, but it should be noted that SH and TH had very similar costs and quality-adjusted life-years (QALYs).² The additional cost of the stapling instrument was largely, but not completely, offset by savings in the length of operating time and hospital stay. In terms

of QALYs, the improvements in quality of life as a result of lower pain levels in the early postoperative period with SH were offset by losses in quality of life as a result of the higher rate of symptoms over the follow-up period. SH thus appeared to be associated with less pain in the immediate postoperative period, but a higher rate of recurrence in the longer term and an increased need for further surgery.¹³ These findings were based on data from small trials, all with methodological flaws, and provided only limited data on quality of life (or, with respect to an economic interpretation, health-state utilities) in the early postoperative period.

At the inception of the eTHoS study there was a reasonable volume of work on grade III and IV haemorrhoids; however, there were limited clinical and economic data regarding SH or TH for grade II haemorrhoids.¹⁴ Members of our group had conducted a small single-centre RCT comparing RBL with SH for grade II haemorrhoids using both clinical and economic outcomes.¹⁵ This had shown a superior clinical effect of SH compared with RBL in terms of recurrence of haemorrhoid symptoms. However, from a health economic standpoint, SH compared with RBL could not be justified, even with a 2-year follow-up. The trend over a longer period, however, suggested that the greater failure rate for RBL may eventually reach a level that justified the increased cost of SH. More robust data on the outcome of RBL have since come from the HubBLE (haemorrhoidal artery ligation versus rubber band ligation for the management of symptomatic second-degree and third-degree haemorrhoids) study¹⁶ comparing HAL with RBL, which shows that RBL, when given as a course of two or three treatments, is as clinically effective as HAL.

There was, therefore, a need for an adequately powered, high-quality multicentre RCT comparing the clinical effectiveness and cost-effectiveness of SH with that of TH in the NHS setting.

Evidence since the inception of the eTHoS study

Since the start of the eTHoS study there have been very few well-designed, prospective large-scale RCTs comparing SH with TH.^{17–19} There were no new trials that included quality-of-life outcomes or looked at the health economics of interventions. These trials included a direct comparison between SH and TH.^{20–22} HAL has become more widely used over the course of the eTHoS study and this is reflected in the number of RCTs examining its clinical effectiveness and utility. Results published in 2016 from the HubBLE study suggest that HAL is no better than repeat RBL, which challenges the place of HAL in the modern surgical management of haemorrhoid disease.¹⁶

A recent network meta-analysis of 98 RCTs, which included 7827 patients and 11 surgical treatments for grade III and IV haemorrhoids, compared a number of surgical and clinical outcomes²³ (Table 1). Patients who had received TH had significantly more postoperative complications than those who had received HAL, LigaSure device and Harmonic scalpel haemorrhoidectomies. Patients who received SH had less pain and resumed normal activities more quickly than those who received TH, but there was a significantly higher chance of recurrent symptoms. The study, however, did not assess patient-reported symptoms nor quality of life.

The aim of the eTHoS study was to assess whether or not SH was more clinically effective and cost-effective than TH for patients with grades II, III and IV haemorrhoids.

The primary objective was to compare patient-reported overall health-related quality of life measured using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L) responses over a period of 24 months.

The secondary objective was to compare subdomains of health [Short Form questionnaire-36 items (SF-36) scores, pain and symptoms], disease recurrence, complication rates, direct and indirect costs to the NHS and cost-effectiveness (measured in terms of incremental cost per QALY, when QALYs are derived from responses to the EQ-5D-3L and the SF-36).

TABLE 1 Surgical treatments with the highest probability of ranking from best to worst (1st to 11th) for the outcomes of interest

Outcome	Ranking										
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
Post-operative complications	Harmonic; $p = 0.447$	Harmonic; $p = 0.351$	LigaSure; $p = 0.291$	LigaSure; $p = 0.344$	Stapled; $p = 0.263$	Stapled; $p = 0.365$	Open; $p = 0.377$	Open; $p = 0.295$	Closed; $p = 0.321$	Closed; $p = 0.352$	Radiofrequency; $p = 0.484$
Post-operative bleeding	Submucosal; $p = 0.405$	THD; $p = 0.334$	THD; $p = 0.332$	Harmonic; $p = 0.186$	LigaSure; $p = 0.254$	LigaSure; $p = 0.240$	Open; $p = 0.216$	Open; $p = 0.297$	Stapled; $p = 0.293$	Radiofrequency; $p = 0.259$	Radiofrequency; $p = 0.498$
Reoperation	THD; $p = 0.710$	Laser; $p = 0.312$	Harmonic; $p = 0.300$	Stapled; $p = 0.334$	Open; $p = 0.257$	Open; $p = 0.355$	Closed; $p = 0.390$	Radiofrequency; $p = 0.594$	n/a*	n/a	n/a
Duration of surgery	Radiofrequency; $p = 0.539$	Harmonic; $p = 0.381$	Harmonic; $p = 0.276$	Stapled; $p = 0.293$	Stapled; $p = 0.314$	THD; $p = 0.293$	THD; $p = 0.537$	Open; $p = 0.887$	Closed; $p = 0.498$	Closed; $p = 0.490$	Laser; $p = 0.909$
Operative blood loss	Bipolar scissors; $p = 0.707$	LigaSure; $p = 0.280$	LigaSure; $p = 0.380$	Stapled; $p = 0.300$	Stapled; $p = 0.313$	Laser; $p = 0.752$	THD; $p = 0.335$	Closed; $p = 0.481$	Open; $p = 0.423$	n/a†	n/a
Length of hospital stay	Radiofrequency; $p = 0.620$	Submucosal; $p = 0.376$	THD; $p = 0.308$	Stapled; $p = 0.392$	LigaSure; $p = 0.228$	LigaSure; $p = 0.363$	Open; $p = 0.296$	Open; $p = 0.308$	Closed; $p = 0.220$	Closed; $p = 0.428$	Laser; $p = 0.392$
Time to first bowel movement (days)	THD; $p = 0.853$	LigaSure; $p = 0.533$	Harmonic; $p = 0.470$	Stapled; $p = 0.566$	Open; $p = 0.596$	Open; $p = 0.263$	Bipolar scissors; $p = 0.569$	n/a†	n/a	n/a	n/a
Time to normal activities (days)	THD; $p = 0.478$	Stapled; $p = 0.370$	Stapled; $p = 0.333$	LigaSure; $p = 0.262$	LigaSure; $p = 0.310$	LigaSure; $p = 0.198$	Open; $p = 0.183$	Open; $p = 0.339$	Open; $p = 0.284$	Closed; $p = 0.322$	Radiofrequency; $p = 0.315$
Pain on day 1	THD; $p = 0.584$	Starion; $p = 0.269$	Stapled; $p = 0.292$	Stapled; $p = 0.255$	LigaSure; $p = 0.292$	LigaSure; $p = 0.277$	Radiofrequency; $p = 0.254$	Closed; $p = 0.427$	Open; $p = 0.422$	Submucosal; $p = 0.480$	n/a§
Pain on day 7	THD; $p = 0.295$	Stapled; $p = 0.342$	Stapled; $p = 0.230$	LigaSure; $p = 0.222$	LigaSure; $p = 0.194$	Closed; $p = 0.231$	Open; $p = 0.242$	Open; $p = 0.285$	Submucosal; $p = 0.382$	n/a¶	n/a
Recurrence of haemorrhoids	Submucosal; $p = 0.381$	Radiofrequency; $p = 0.358$	LigaSure; $p = 0.277$	LigaSure; $p = 0.315$	Closed; $p = 0.273$	Open; $p = 0.383$	Stapled; $p = 0.287$	Stapled; $p = 0.649$	THD; $p = 0.785$	n/a¶	n/a
Recurrent haemorrhoidal symptoms	Laser; $p = 0.530$	LigaSure; $p = 0.333$	Closed; $p = 0.296$	THD; $p = 0.282$	Open; $p = 0.448$	Stapled; $p = 0.482$	Harmonic; $p = 0.467$	n/a#	n/a	n/a	n/a

n/a, not applicable; THD, transanal haemorrhoid dearterialisation.

Treatment not included in the analysis for this outcome: *Starion™, submucosal, bipolar scissors; †submucosal, radiofrequency; ‡laser, Starion, submucosal, radiofrequency; §bipolar scissors; ¶Starion™, bipolar scissors; #Starion™, submucosal, radiofrequency, bipolar scissors.

'n/a' has been used when fewer than 11 treatments were analysed for these outcomes.

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Chapter 2 Study design

The eTHoS study was a large multicentre UK pragmatic RCT to assess whether or not SH is more clinically effective and cost-effective than TH for people presenting with haemorrhoids (grades II, III and IV).¹

Participants

Potential participants were adults referred to NHS hospitals for consideration of surgical treatment and identified according to the inclusion and exclusion criteria specified below. Participants could have previously had RBL or HAL, but not undergone any other form of haemorrhoid surgery.

Inclusion criteria

- Patients with circumferential haemorrhoids of grades II, III or IV.
- Patients aged ≥ 18 years.
- Written informed consent obtained.

Exclusion criteria

- Previous surgery for haemorrhoids (traditional or stapled, except RBL or HAL).
- Previous surgical treatment for anal sphincter injury repair or symptomatic incontinence or perianal sepsis.
- Known inflammatory bowel disease.
- Malignant gastrointestinal disease, within the last 5 years.
- Medically unfit for surgery or for completion of the study.
- Pregnant women.

Participants were randomised to one of the two study groups on a 1 : 1 basis. The randomisation minimisation algorithm used centre, grade of haemorrhoidal disease (II, III or IV), baseline EQ-5D-3L score (categorised as < 0.6 , 0.6 to < 0.8 and 0.8 to 1.0) and sex. A remote telephone interactive voice response randomisation application, hosted by the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU) at the University of Aberdeen, was used to perform the randomisation.

The main criterion for selection of NHS hospital sites across the UK where participant recruitment could take place was that each hospital centre had at least two members of staff to occupy two key research roles. One was that of the research role – a (co-investigating) colorectal consultant; the other was that of a local recruitment officer, for example a nurse or junior doctor. In exceptional circumstances the colorectal consultant performed both roles. At each centre there may have been more than one colorectal consultant (co-investigator) who was fully eTHoS trained and actively screening potential patients (for eligibility) and for subsequent recruitment onto the study. At each centre one of these consultants assumed the leading role of local lead colorectal surgeon for the eTHoS trial. A total of 32 UK NHS sites took part in the study. These were NHS Highland and Islands, Inverness; NHS Grampian, Aberdeen; North Tees and Hartlepool Hospitals NHS Foundation Trust, Stockton-on-Tees; Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield; County Durham and Darlington NHS Foundation Trust, Durham; Leeds Teaching Hospitals NHS Trust, Leeds; Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich; Central Manchester University Hospitals NHS Foundation Trust, Manchester; Chelsea and Westminster Hospital NHS Foundation Trust, London; NHS Greater Glasgow and Clyde, Glasgow; Betsi Cadwaladr University Health Board, Rhyl; Oxford University Hospitals NHS Foundation Trust, Oxford; Aintree University Hospital NHS

Foundation Trust, Liverpool; Dr Gray's Hospital, Elgin; Brighton and Sussex University Hospitals NHS Trust, Brighton; South Tees Hospitals NHS Foundation Trust, Middlesbrough; Calderdale and Huddersfield NHS Foundation Trust, Huddersfield; Wirral University Teaching Hospital, Upton, Wirral; Croydon Health Services NHS Trust, Croydon; Royal Free London NHS Foundation Trust, London; The Mid Yorkshire Hospitals NHS Trust, Wakefield; Royal Cornwall Hospitals NHS Trust, Truro; The Hillingdon Hospitals NHS Foundation Trust, London; Bwrdd Iechyd Aneurin Bevan Health Board, Wales; Weston Area Health NHS Trust, Somerset; Derby Teaching Hospitals NHS Foundation Trust, Derby; NHS Forth Valley, Stirling; Gateshead Health NHS Foundation Trust, Gateshead; Colchester Hospital University NHS Foundation Trust, Colchester; Basildon and Thurrock University Hospitals NHS Foundation Trust, Basildon; United Lincolnshire Hospitals NHS Trust, Lincoln; and University Hospital of South Manchester NHS Foundation Trust, Manchester.

Study interventions

Eligible participants who consented were placed on the appropriate waiting list by the treating colorectal surgeon or his/her designated team member. Participants received the allocated intervention to which they were randomised:

- stapled haemorrhoidopexy
- traditional excisional haemorrhoidectomy.

Each centre's participating surgeons had undergone appropriate recognised training for both SH and TH surgery. Surgery was performed by surgeons in training: either independently, if signed off by their supervising consultant, or under the direct supervision of their consultant. Pre- and postoperative care followed the respective surgeon's and/or centre's standard policies.

Outcome measures

Primary outcome measures

Patient reported

The primary outcome was quality of life gained over the follow-up period [area under the curve (AUC) derived from EQ-5D-3L measurements taken from patient questionnaires distributed at baseline, 1 week, 3 weeks, 6 weeks (postoperatively), 12 months, (EQ-5D-3L only at 18 months if not completed at 12 months) and 24 months post randomisation].

Participants had the opportunity to complete the questionnaires on a secure portal on the eTHoS trial website using log-in details provided by the study team. In the event that the postal questionnaires were not returned or completed via the website, for the 1- and 3-week questionnaires, participants were telephoned to obtain the missing data. Postal reminders were issued if there was no response to the 6-week, 12-month and 24-month questionnaires. A final reminder followed if there was no response to the subsequent reminder. This reminder was shortened to include only the EQ-5D-3L questionnaire.

Health economic

Incremental cost per QALY gained, with QALYs based on the responses to the EQ-5D-3L at 24 months, was measured. QALYs were calculated from participant responses to the EQ-5D-3L completed at baseline, 1 week, 3 weeks and 6 weeks post surgery, and 12 (or 18) and 24 months post randomisation. Costs were collected at baseline, 6 weeks, and 12 and 24 months after randomisation. Participants also provided information about their use of health services via the health-care utilisation questions within the eTHoS trial patient questionnaires (see *Appendix 1*).

Secondary

Patient reported

Patient-reported secondary outcomes were:

- generic health profile as measured by the SF-36 and the EQ-5D-3L
- visual analogue scale (VAS) pain score
- Cleveland Incontinence Score (CIS)
- Haemorrhoid Symptom Score (HSS)
- postoperative analgesia consumption
- recurrence of haemorrhoids
- tenesmus.

Clinical

The clinical secondary outcomes were intra-operative and postoperative complications, including:

- haemorrhage
- requirement for blood transfusion
- anal stenosis
- anal fissure
- urinary retention (which requires catheterisation)
- residual anal skin tags
- difficult defaecation
- wound discharge
- pelvic sepsis
- pruritus
- recurrence of haemorrhoids.

Economic

The economic secondary outcomes were:

- costs based on NHS resource use data
- length of hospital stay
- use of health services for haemorrhoid-related events or treatments
- patient costs (treatments, travel to health services, sick leave)
- need for alternative management for haemorrhoids (e.g. surgery, drugs)
- other use of health services, such as:
 - visits to general practitioner (GP)
 - visits to practice nurse
 - visits to colorectal surgeon
- QALYs estimated from the EQ-5D-3L at 24 months
- cost-effectiveness analysis (incremental cost per case of SH and TH excision avoided).

Chapter 3 Methods

Research ethics and regulatory approvals

The eTHoS study was given favourable ethics approval by the North of Scotland Research Ethics Committee (REC) on 18 June 2010 subject to receiving individual research approvals from each host organisation prior to the commencement of the study at site (reference number 10/20802/17). The study was co-sponsored by NHS Highland and the University of Aberdeen. The study was registered and was given an International Standard RCT Number (ISRCTN80061723).

Project management group

The study was supervised by a project management group (PMG). This consisted of the grant holders and representatives from the study office, who provided day-to-day support for the study. Observers were invited to attend at the discretion of the PMG. The PMG met every 6 months, on average, during the course of the study.

Study oversight committees

The study Data Monitoring Committee (DMC) comprised three independent individuals who met initially at the beginning of the study when terms of reference and other committee procedures were agreed. The committee then met an additional four times during the course of the study to monitor unblinded baseline and outcome data provided by the study statistician and details of serious adverse events (SAEs). The DMC reported any recommendations to the chairperson of the Trial Steering Committee (TSC). The TSC comprised four independent individuals who oversaw the study. At the invitation of the chairperson, grant holders and observers/members of the host university (University of Aberdeen) and the funder (HTA programme) could also attend. Terms of reference for the TSC were agreed at the commencement of the study and the group met annually throughout the duration of the study. The terms of reference for the DMC and TSC can be accessed on request from the eTHoS study office.

Patient and public involvement

An independent patient and public involvement representative was a member of the TSC. A patient representative was also involved in the grant application and throughout the study as a grant holder. Patient and public involvement was sought in the development of the participant newsletter. Both members reviewed the paperwork and provided constructive feedback in its development.

Participants

Study flow

The flow of participants through the study is detailed in *Figure 1*.

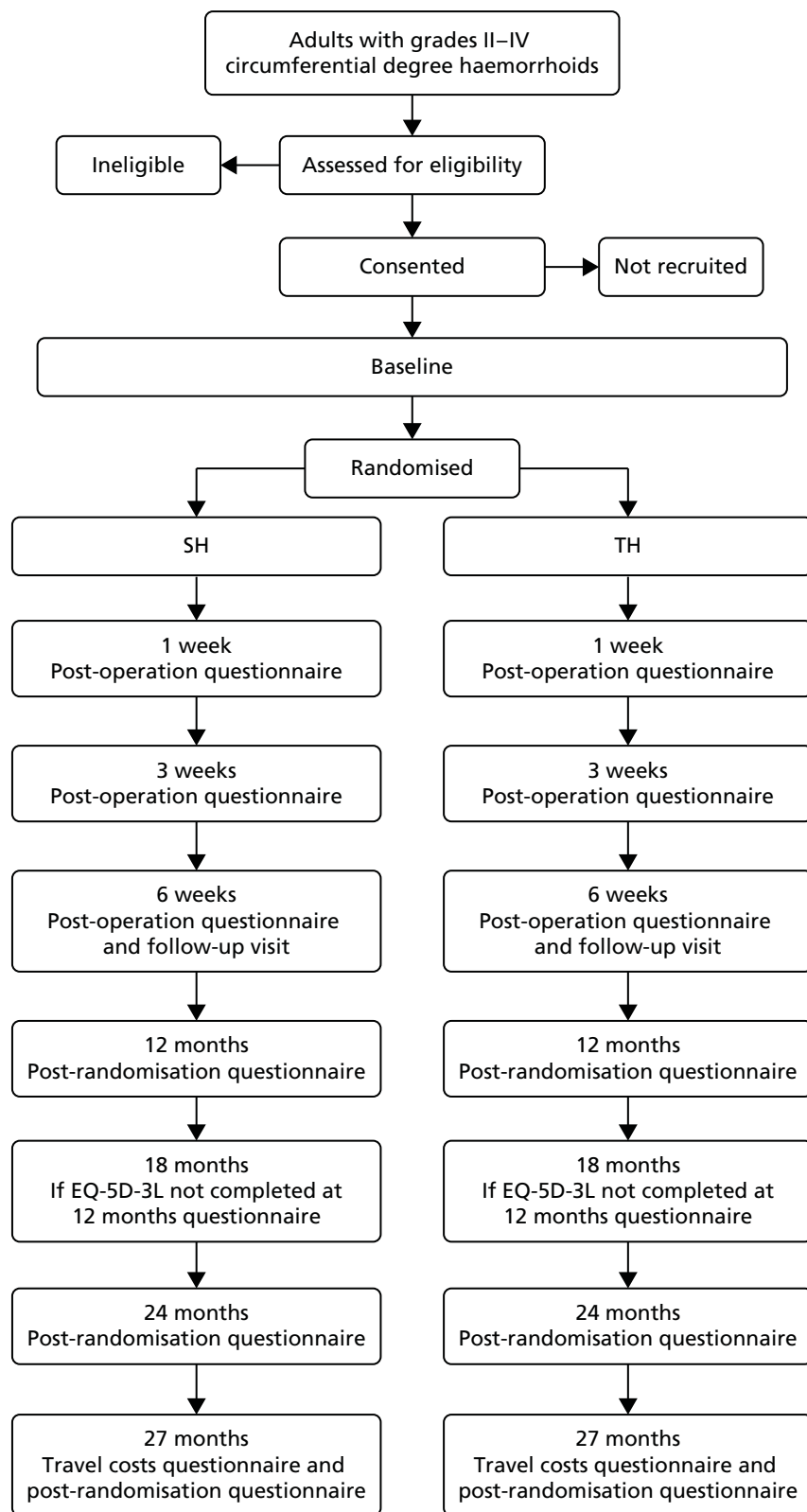


FIGURE 1 Participant study flow.

Identification of patients and recruitment

Patients were identified by colorectal clinicians in participating sites, and were supported by local clinical research teams.

Colorectal clinicians assessed the eligibility of the participants for surgery according to standard practice. At the initial consultation, the colorectal clinician discussed the various treatment options available and provided information regarding the eTHoS study. Risks and benefits of all treatments were also discussed as part of standard clinical practice. Patients who had undergone RBL or HAL but still had symptoms were eligible for the study. Patients who had received any other form of haemorrhoid surgery were excluded from the study. Participants who expressed a strong preference for one of the interventions were also excluded. Identified eligible patients were then given a patient information leaflet (PIL; see *Appendix 2*), which contained details of the study and context. The clinician, or a trained member of the local clinical team, was able to answer any questions/discuss the study with the potential participants. Patients were encouraged to take time to read through the PIL and to take it home if they should wish. If the patient agreed to be contacted at home, then a member of the local research team would call to discuss the study. Patients who gave verbal agreement to take part in the study were then requested to complete documents [consent form and baseline questionnaire, which collected data on the EQ-5D-3L, the SF-36, the CIS and the HSS, and patient preference for surgery outcomes (see *Appendices 2 and 3*)] and return these by post to the local study team at their treating hospital or bring them when they returned to hospital for preoperative assessment or at the time of the operation. The consent form was then countersigned on receipt by the local study team member.

Patients who were able to make a decision to join the study while they were at the initial consultation were provided with the eTHoS study participant baseline questionnaire. This was completed only once a patient was eligible and happy to take part in the study and had signed the consent form. Contact details for both the local and central team were provided on the PIL. Further checking against eligibility criteria was performed by local research staff. Current clinical status was also captured on the baseline case report form (CRF) (see *Appendix 3*).

Following full written consent and baseline data completion, patients were randomised as near to their surgery date as possible. For those patients who did not consent to participate, an 'Ineligible/Declined' form (see *Appendix 3*) was completed by a local study team member, detailing non-personal data, including the reason(s) for the participant declining (if provided), or the ineligibility criterion. These data were recorded on the study database to inform the consort.

Randomisation

Participants were randomised to one of the two study groups on a 1 : 1 basis. The minimisation algorithm used centre, grade of haemorrhoidal disease (II, III or IV), baseline EQ-5D-3L score and sex. A remote telephone interactive voice response randomisation application hosted by CHaRT, HSRU at the University of Aberdeen was used to perform randomisation. The first participant was randomised on 13 January 2011 and the final participants were randomised on 1 August 2014 when the randomisation system was closed.

Study interventions

Eligible participants who consented were placed on the appropriate waiting list by the treating colorectal surgeon or his/her designated team member. Most participants received the allocated intervention, which was either SH or TH. Some received alternative treatment or did not receive treatment; however, participants were followed up regardless of the intent-to-treat analysis. Treatment data were captured on the hospital and surgery CRF (see *Appendix 3*). Each centre's participating surgeons had to have undergone

appropriate recognised training for both SH and TH. Surgeries were performed by surgeons in training; either independently, if signed off by their supervising consultant, or under the direct supervision of their consultant. Pre-operative and postoperative care followed the respective surgeon's and centre's standard care policies. Although the two procedures being compared are offered as routine care, not all sites provided postoperative information (what to expect after the haemorrhoid treatment) to participants. Therefore, we prepared a participant postoperative leaflet that sites could make available to participants if they wanted to (see *Appendix 2*).

Data collection

Follow-up consisted of clinical follow-up at 6 weeks after treatment. Postal questionnaires were distributed at 1 week, 3 weeks and 6 weeks after treatment, and 12 months (or 18 months if EQ-5D-3L not completed at 12 months) and 24 months after randomisation (*Table 2*). The main outcome assessment was planned at 24 months' (from the date of randomisation) follow-up.

Consent was sought from all participants recruited to the study to be flagged for notification of haemorrhoidal recurrence. To evaluate long-term safety, the participants who had further haemorrhoidal surgery were identified via registry databases: Hospital Episode Statistics (HES) in England, Patient Episode Database Wales (PEDW) in Wales and Information Services Division (ISD) data in Scotland, when all participants had reached 12 months post randomisation.

Safety reporting

We reported SAEs in accordance with the guidance from the National Research Ethics Service, which is a subdivision of the National Patient Safety Agency. As such, non-SAEs were not collected or reported. All SAEs were recorded on the SAE report form (see *Appendix 3*). In addition, SAE forms recorded all deaths during the course of the study whether or not these were related to the research procedures. The following occurrences were potentially expected: intraoperative occurrences associated with the intervention, including anaesthetic-related problems, intraoperative instrument failure, damage to adjacent organs and bleeding. Possible (expected) occurrences associated with either type of surgery occurring at any time during the study included haemorrhage, requirement for blood transfusion, anal stenosis, anal fissure, pain, urinary retention, residual anal skin tags, anal fistula, prolapse, difficult defaecation, faecal urgency, wound discharge, pelvic sepsis, systemic complications and pruritus.

The details of any of the occurrences listed above were recorded on the CRFs and on participant-completed questionnaires and reported to the DMC in annual reports, but were not recorded as a SAE unless defined as an event occurring to a research participant that was related (resulted from administration of any of the research procedures) and was expected or unexpected, which caused death, was life-threatening, required hospitalisation, resulted in significant incapacity/disability or was otherwise considered medically significant by the investigators. Expected and unexpected SAEs were recorded.

Change of status/withdrawal

Participants remained on the study unless they chose to withdraw consent or if the principal investigator, chief investigator or study office felt that it was no longer appropriate for the participant to continue (i.e. the participant became unable to complete the study documentation). Reasons for participant withdrawal from the study were recorded on the 'withdrawal/change of status' form (see *Appendix 3*). Participants could withdraw from treatment but remain in the study for follow-up questionnaires and/or to have relevant outcome data collected from NHS records if consent remained for this.

TABLE 2 The eTHoS study data collection

Outcome	Time point							
	Baseline	Surgical form	1 week post treatment	3 weeks post treatment	6 weeks post treatment	12 months post randomisation	24 months post randomisation	27 months post randomisation
Clinical status	✓							
Surgical details		✓						
Patient preference	✓							
6 weeks' clinical follow-up					✓			
EQ-5D-3L ^a	✓		✓	✓	✓	✓	✓	
SF-36	✓				✓	✓	✓	
Pain VAS			✓	✓	✓			
HSS	✓				✓	✓	✓	
CIS	✓				✓	✓	✓	
Health-care Utilisation questions						✓	✓	
Travel costs questionnaire								✓
Recurrence						✓	✓	
Analgesia question			✓	✓	✓			
DCE								✓
Hospital Statistics for further surgery						✓		

DCE, discrete choice experiment.

^a Outcome also collected at 18 months for non-responders at 12 months.

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Data management

Clinical data were collected at the individual hospital centres using hospital-based records and hard-copy CRFs (see *Appendix 3*). Clinical data were then input onto the eTHoS study database by local researchers using an electronic web-based data capture system [in addition relevant clinical data being collected from registry databases (HES, PEDW and ISD)]. Extensive range and consistency checks enhanced the quality of the data. Staff in the study office provided periodic data queries to local research staff to ensure that the data were as complete and accurate as possible. Questionnaires returned by post to the study office were entered onto the database by data-trained members of the central research team.

Data collected during the course of the research were kept strictly confidential and accessed only by members of the study team. Participants' details were stored on a secure password-protected and user-specific database under the guidelines of the 1998 Data Protection Act,²⁴ including encryption of any identifiable data. Participants were allocated an individual-specific study number and all data, other than personal data, were identified only by this unique study number.

The content of approximately 10% of CRFs and participant questionnaires entered at sites were checked to ensure accuracy. To ensure that sites had understood the data-entry processes and that they were efficiently entering the data, a sample from the first CRFs entered by each site were selected. Further paper CRFs and questionnaires were selected at random. This was completed at the study office (a copy of the paper forms were sent/faxed from the individual sites to the University of Aberdeen to facilitate this). An error rate of < 5% required no further action; however, if the error rate was > 5%, a 100% check of all forms from that site was undertaken.

Some questionnaires were returned directly to the University of Aberdeen. A 10% random sample of questionnaires returned to the study office were checked by a different data co-ordinator/clerk than the person responsible for the initial data entry, and the action on identified error rate was identical to that described above.

Statistical methods and study analysis

Ground rules for the statistical analysis

Study analyses followed the statistical analysis plan agreed in advance by the TSC. The main statistical analyses were based on all randomised participants, irrespective of subsequent compliance with the treatment allocation. Statistical significance was at the two-sided 5% level with corresponding confidence intervals (CIs) derived.

Sample size

Data on the 24-month AUC (QALYs) for the EQ-5D-3L scores in this patient group were sparse, but an effect size of 0.25 standard deviations (SD) was considered a worthwhile difference in quality-of-life measures. A sample size of 338 per group was required to provide a 90% power to detect a difference in the mean area under the quality-of-life AUC curve with a significance level of 5% (two-sided alpha). To allow for 15% non-response in the outcome, we required 400 participants in each treatment group. This sample size would also give 90% power to assess differences in the secondary outcome of recurrence between the two interventions from around 10% to around 4%. This difference is supported by a recent systematic review,⁹ which showed a non-statistical trend of higher recurrence in the SH group than in the TH group.

Primary/secondary outcome analysis

The primary outcome, AUC (measured by the EQ-5D-3L), was generated for each participant using the trapezoidal rule and analysed using linear regression. The analysis was adjusted for the minimisation variables, centre was accounted for by using cluster robust standard errors while the others were fixed effects. To be included in the primary analysis, participants had to have at least one short-term measure

(1 week, 3 weeks or 6 weeks post surgery) and at least one long-term measure (12, 18 or 24 months post randomisation). In the sensitivity analysis, missing EQ-5D-3L data were estimated using a multiple imputation (MI) by chained equations using the 'ice' Stata® version 14 (StataCorp LP, College Station, TX, USA) command. It also included assessment of the robustness of the treatment effect estimates by altering the minimum number of EQ-5D-3L values needed for each participant and also compliance (using a per-protocol analysis that comprised those participants who received their allocated intervention). Secondary analyses for the primary outcome included the EQ-5D-3L AUC over 6 weeks and 12 months.

Secondary outcomes (SF-36, CIS and HSS) were analysed using linear mixed models with adjustment for minimisation variables. Tenesmus was analysed with the chi-squared test for trend and further surgical intervention was analysed with the chi-squared test. All other secondary outcomes were analysed using either logistic or linear regression. Continuous variables were summarised with mean (SD) or median [interquartile range (IQR)], whereas discrete variables were number and percentages. All analyses were assessed at the two-sided 5% significance level and done using Stata software.

Planned subgroup analyses

Subgroup analyses explored the possible treatment effect modification of clinically important factors (haemorrhoidal grade and sex) through the use of treatment-by-factor interaction, all using a stricter two-sided 1% level of statistical significance.

Patient preference analyses

Baseline data were summarised by treatment preference based on surgical outcome scenarios and the primary and secondary outcomes were analysed using linear regression adjusted for patient preference and minimisation variables. Presence of a treatment-by-preference interaction was assessed. In addition, associations between preference and drop-out were analysed. The patient preference analysis is reported in *Chapter 9*.

Timing and frequency of analyses

A single principal analysis was carried out when the final participant reached the 24-month time point.

Economics methods

Introduction

Although a de novo economic model was planned to assess the long-term cost-effectiveness (assessed in terms of incremental cost per QALY) and net benefits of SH and TH, the results of the study-based economic evaluation in conjunction with the clinical findings rendered the planned modelling unnecessary. Therefore, the following section describes the methods for the study-based economic evaluation. The question to be addressed by the economic evaluation was 'what are the relative cost-effectiveness (assessed in terms of incremental cost per QALY) and net benefits of SH and TH?'. The cost-effectiveness analysis follows the National Institute for Health and Care Excellence (NICE)'s reference case²⁵ and the International Society for Pharmacoeconomics and Outcomes Research's recommendations on conducting economic evaluations alongside clinical trials.²⁶ A secondary analysis also assessed cost to participants. The methods and analysis for the within-trial analysis are described below. The perspective of study was that of the health service provider (the NHS) and the costs are expressed in pounds sterling for the financial year 2014–15.²⁷ Costs and benefits incurred in the second year were discounted at a rate of 3.5% per annum.²⁵ The follow-up period for the economic analysis was 24 months.

Within-trial analysis

Health service use was recorded prospectively, and retrospectively, for each participant. Intervention resource use was collected prospectively for every participant in the study using questionnaires at baseline and CRFs, and follow-up resource use was collected retrospectively at 6 weeks, and 12 and 24 months (see *Appendix 1*). The underlying aim was to keep economic data collection as parsimonious as possible in

order to minimise the burden on the participants and the effect on response rates. A postal questionnaire of all participants was used to ascribe participant costs to typical episodes of health service use, and was initially sent at 18 months post randomisation (see *Appendix 1*), but this was changed during the course of the study to 27 months post randomisation. This was to allow a shortened third reminder to be issued at 18 months for the 12-month questionnaire.

The areas of resource use considered comprised four broad areas:

- intervention resource use
- secondary care resource use
- primary care resource use
- resource use directly incurred by the participants.

Intervention resource use

The intervention resource use was recorded on a per-patient participant basis. The resources used to provide surgery were established by consulting with relevant staff at participating centres (surgeons, theatre nurses, business managers) and members of the study team to elicit information on:

- equipment, such as the type of stapler used
- frequency of use of said equipment
- consumables used during surgery, such as surgical trays
- staff mix of the surgical team (e.g. grade of the operating surgeon, grade of the anaesthetist, grade and number of nurses).

In addition to this, the operative information was collected on the CRFs and provided details of the grade of staff involved and the duration of procedure. Length-of-stay information was elicited for each participant through the CRFs by collecting the date of admission and discharge. For the initial intervention, data cost estimation focused on those resources that differed between the two interventions, that is, it was assumed that there would be no difference in time in recovery or time on the ward following the procedure (for those managed as day cases).

Other secondary care resource use

The use of subsequent care, such as inpatient stay (duration of stay), reoperation or other surgical interventions (SH or TH) and outpatient visits over the study follow-up period, was obtained from the CRFs (6 weeks) and patient questionnaire (12 and 24 months).

Primary care resource use

All primary care resource use, such as general practice doctor and nurse contacts and medications prescribed to treat haemorrhoids, was obtained from the participant questionnaire administered at 12 and 24 months.

Derivation of costs

The costs of the health service utilisation were estimated by combining resource use data with unit costs of resource use. Unit costs were based on study-specific estimates in combination with data from standard sources. Unit costs for the equipment used in stapling were obtained from the manufacturers of the products through personal communication with sites using the equipment or from published price lists. *Table 3* details the unit costs used, the source of the estimate and any assumptions used to derive them.

Unit costs for outpatient visits were obtained from the NHS reference costs for the period of 2014–15.²⁷ Unit costs for GP visits were obtained from the Personal Social Services Research Unit²⁸ unit costs of social care. The unit costs of anaesthetic drugs, such as propofol used in the operation and post surgery, were derived from the *British National Formulary*.²⁹ For each participant the number of visits was multiplied by the appropriate unit cost. These costs were summed to produce a total cost per patient. The unit cost of the type of stapler used in the intervention was based on the cost of the stapler specified for each patient.

TABLE 3 Unit costs for resources used in the within-trial economic analysis

Resource item	Unit cost (£)	Comments	Source
Stapler			
Ethicon PPH03 (Johnson & Johnson, New Brunswick, NJ, USA)	442.01	Box of three – £1105.04 excluding VAT	NHS Scotland and NHS England Hub prices (Ewan McDonald, NHS Grampian, 2016, personal communication)
Chex CPH 32	276.00	Box of three – £690 excluding VAT	NHS Scotland and NHS England Hub prices
EEA™ Staplers with DST™ Series technology (Covidien Ltd, Dublin, Ireland)	269.62	Box of three – £674.06 excluding VAT	NHS Scotland and NHS England Hub prices
Surgeon and anaesthetist			
Consultant	2.30 per minute	£138 per hour	PSSRU (2015) ²⁸
Specialty doctors and associate specialists	2.13 per minute	£128 per hour	PSSRU (2015) ²⁸
Surgical trainee	1.20 per minute	£72 per hour	PSSRU (2015) ²⁸
Fellow	0.85 per minute	£51 per hour	PSSRU (2015) ²⁸
Nurses			
Band 5	0.72 per minute	£43 per hour	PSSRU (2015) ²⁸
Band 6	0.85 per minute	£51 per hour	PSSRU (2015) ²⁸
Anaesthetic drug cost			
General	14.31	Various drugs (propofol)	BNF (2016) ²⁹
General and block	15.17	Various drugs (bupivacaine hydrochloride)	BNF (2016) ²⁹
Spinal	2.25	Various drugs (lidocaine, etc.)	BNF (2016) ²⁹
Interventions at 6 weeks			
Outpatient appointment	122.5	Average colorectal specialty	<i>NHS Reference Costs 2014 to 2015</i> ²⁷
Re-admissions after intervention ^a	201	Admitted VB07Z emergency medicine, category 2	<i>NHS Reference Costs 2014 to 2015</i> ²⁷
Emergency outpatient visits ^b	162	Emergency medicine, category 2 investigation with category 2 treatment	<i>NHS Reference Costs 2014 to 2015</i> ²⁷
Further interventions at 6 weeks, for example haemorrhoidectomy	1106	Day case FZ22E intermediate anal procedures, aged ≥ 19 years, with complications score of 0	<i>NHS Reference Costs 2014 to 2015</i> ²⁷
Proctoscopy	10.99	–	–
Medicines, for example Movicol® (Norgine, Pharmaceuticals Ltd, Uxbridge, UK)	Various	Based on patient report	BNF (2015) ³⁰
Glyceryl trinitrate paste	39.30	Price per 30-g tube	BNF (2015) ³⁰
Diltiazem paste	78.83	Price for 2% diltiazem cream per 30-g tube	BNF (2015) ³⁰

continued

TABLE 3 Unit costs for resources used in the within-trial economic analysis (*continued*)

Resource item	Unit cost (£)	Comments	Source
Repeat SH and TH further interventions			
Day case	751	FZ23A minor anal procedures, aged ≥ 19 years	NHS Reference Costs 2014 to 2015 ²⁷
Day case	1118	Day case FZ22D intermediate anal procedures, aged ≥ 19 years, with complications score of 1 or 2	NHS Reference Costs 2014 to 2015 ²⁷
Post discharge events			
Doctor visits	44	Per 11.7-minute consultation, including qualification costs	PSSRU (2015) ²⁸
Nurse visits	11	Per 15.5-minute consultation, including qualification costs	PSSRU (2015) ²⁸
Medications			
Analgesic	Various	As reported by participants	BNF (2016) ²⁹
Laxative	Various	As reported by participants	BNF (2016) ²⁹
Antibiotics	Various	As reported by participants	BNF (2016) ²⁹
RBL	181	FZ23A minor anal procedures, aged ≥ 19 years, procedures in outpatients	NHS Reference Costs 2014 to 2015 ²⁷

BNF, *British National Formulary*; PSSRU, *Personal Social Services Research Unit*; VAT, *value-added tax*.

a These were visits for postoperative complications, such as bleeding, that required hospitalisation.

b These were emergency visit postoperative complications, such as pain, that did not result in admission.

Measurement of resource utilisation for participants' management of haemorrhoids

Participant resource use comprised three main elements: self-purchased health care; travel costs for making return visit(s) to NHS health care; and time costs of travelling and attending NHS health care.

- Self-purchased health care is likely to include items such as prescription costs and over-the-counter medications. Information about these was collected through the health-care utilisation questions.
- Estimation of travel costs requires information from participants about the number of visits to, for example, their GP or consultant (estimated from the health-care utilisation questions) and the cost to the participant of making the return journey to each type of health-care provider. The latter was collected using the participant cost questionnaire (see *Appendix 1*).
- The cost of participant time was estimated in a similar manner. The participant was asked, in the participant cost questionnaire, how long they spent travelling to, and attending, their last visit to each type of health-care provider. Participants were also asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health-care provider. Time away from displaced activities was measured in hours and also costed using standard economic conventions, for example the Department of Transport estimates for the value of leisure time. The unit costs used in the estimation of patient time and travel costs are all summarised in *Table 4*.

Quality of life

Clinical effectiveness in the economic analysis was measured in terms of QALYs. The EQ-5D-3L³⁶ generic quality-of-life instrument was administered to all study participants at baseline, at 1 week, 3 weeks and 6 weeks, and at 12 months and 24 months. The EQ-5D-3L measure divides health status into five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

TABLE 4 Unit costs of participants and companion time, travel and loss of earnings

Activity	Unit costs (£)	Assumptions	Source of data
Cost per mile travelled by car	0.45 per mile	HMRC-approved mileage rate	HMRC ³¹
Car parking charges	Various	As stated by participant	Participant questionnaire
Cost of public transport (fares)	Various	As stated by participant	Participant questionnaire
Cost of non-emergency patient transport (ambulance)	44.50 per journey	–	<i>NHS Reference Costs 2014 to 2015</i> ²⁷
Cost related to participant and companion time			
Paid work	13.47 per hour	Based on average economic wage per week of £528 assuming 39.2 hours per working week	ONS's <i>Average Weekly Earning Time Series Dataset</i> (2015) ³²
Housework	10.66 per hour	Cost of housework in the NHS (assumed annual salary of £21,000 gross)	NHS Pay Review Body (2015) ³³
Child care	13.47 per hour	As paid work	ONS's <i>Average Weekly Earning Time Series Dataset</i> (2015) ³²
Caring for family/friend	13.47 per hour	As paid work	ONS's <i>Average Weekly Earning Time Series Dataset</i> (2015) ³²
Voluntary work	13.47 per hour	As paid work	ONS's <i>Average Weekly Earning Time Series Dataset</i> (2015) ³²
Leisure activities	6.62 per hour	Value for non-working time (2010 prices inflated to 2015)	<i>WebTAG: TAG Data Book, December 2015</i> ³⁴
Retired	6.62 per hour	Value for non-working time (2010 prices inflated to 2015)	<i>WebTAG: TAG Data Book, December 2015</i> ³⁴
Unemployed	6.62 per hour	Value for non-working time (2010 prices inflated to 2015)	<i>WebTAG: TAG Data Book, December 2015</i> ³⁴
Disabled (long-term unrelated to haemorrhoids)	6.62 per hour	Value for non-working time (2010 prices inflated to 2015)	<i>WebTAG: TAG Data Book, December 2015</i> ³⁴
Incontinence day pads	1.57	Mean monthly cost of nappies (the least expensive) £47.10 (three per day)	Fader <i>et al.</i> , 2008 ³⁵
Incontinence day pads	0.66	Mean monthly cost of nappies (the least expensive) £19.80 (one per night)	Fader <i>et al.</i> , 2008 ³⁵

HMRC, HM Revenue & Customs; ONS, Office for National Statistics; TAG, transport analysis guidance.

Responses to the EQ-5D-3L are presented in graphical format, illustrating percentage of respondents with any or severe problems on each health domain, split by randomised arms of the study. Results are presented in accordance with EuroQoL guidelines.³⁷

Responses to the EQ-5D-3L questionnaires were valued using UK general population tariffs,³⁸ based on the time trade-off technique to generate a utility score for every participant within the study. Quality-of-life data derived from the EQ-5D-3L were combined with mortality data from the study, using the standard assumption that all participants who died during the study will have a utility value of zero from the date of death to the end of follow-up. QALYs were then calculated on the basis of these assumptions using an AUC approach, assuming linear extrapolation of utility between time points.

Quality-of-life data were also collected using the SF-36 questionnaire for comparison. SF-36 data were collected at baseline, 6 weeks, and at 12 and 24 months. The SF-36 is a generic measure obtained from a multipurpose, short-form health survey with 36 items.³⁹ It yields an eight-scale profile of functional health and well-being scores along with psychometrically based physical and mental health summary domains and a preference-based health utility index. These data were converted into a Short Form questionnaire-6 Dimensions (SF-6D) utility index using a published algorithm.⁴⁰ As described above for the EQ-5D-3L, QALYs were also derived from these data and a secondary analysis was used.

Cost-effectiveness analysis methods

Economic analyses were consistent with the methods described for the main statistical analyses (primary outcome). All data analyses were conducted using Stata software. The primary economic analysis was based on the imputed data of all participants as randomised, irrespective of the treatment allocation. There was a substantial number of missing data and this posed problems for data analysis, especially surrounding data reported using participant-completed questionnaires. Therefore, statistical MI of missing data was undertaken. The imputation analysis was performed using Stata's MI procedure.⁴¹ Missing component costs (e.g. cost of primary care, outpatient care) and utility values were imputed at each questionnaire time point (12 and 24 months). The cost-utility analysis was conducted using the MI data. Briggs *et al.*⁴² concluded that imputing the missing data is preferable to a complete or available case analysis.

Components of cost data were imputed based on linear regression models adjusted for minimisation variables, baseline utility and treatment allocation group. Missing utility values were imputed using predictive mean-matching, accounting for the five closest estimates. Chained equations were used for the imputations. The imputation procedure predicted 10 plausible alternative imputed data sets, which was found to be sufficient to provide stable estimates. Analysis of incremental costs and outcomes was undertaken across the 10 imputed data sets and combined to generate one imputed estimate of incremental costs and QALYs. All imputed data sets were plotted on cost-effectiveness acceptability curves (CEACs) using similar methods to the main analyses. Sensitivity analysis was applied in order to assess robustness of the results to realistic variations in the levels of the underlying data and also alternative assumptions, for example QALYs derived from the SF-36.

Data are presented descriptively, and the primary outcome measure was analysed using linear regression with adjustment for the minimisation variables. The minimisation variables are centre, grade of haemorrhoidal disease (II, III or IV), baseline EQ-5D-3L score and sex.

The primary economic analysis presents estimates of the incremental cost per QALY of SH versus TH. The incremental cost-effectiveness ratio (ICER) can be compared with the benchmark willingness-to-pay (WTP) thresholds for cost-effectiveness in the NHS context of £20,000 to £30,000 per QALY gained, as applied by NICE.⁴³ Regression-based methods (as above) were used to estimate difference in costs for care between SH and TH, over the 24-month study period. CIs (95%) were estimated using parametric methods. To facilitate interpretation of the study results, the within-trial economic analysis is also presented in the form of a balance sheet in which differences in terms of benefits and costs of the two study interventions are presented in their natural or clinical units. Item-level costs are presented descriptively, consistent with the data presentation in the effectiveness analyses.

To explore the skewness of data, a generalised linear model was used; this model allows for heteroscedasticity by selecting an appropriate distributional family for the data.⁴⁴ The family offers alternative specifications to reflect the relationship between the mean and the variance of the estimates under considerations. The most appropriate distributional family was selected by (1) performing a modified Parks test, which identified two potentially viable distributional families for costs, namely Gaussian or Gamma; and (2) consulting the Akaike information criterion, which identified a Gaussian model with an identity link as having the lowest Akaike information criterion score and the most appropriate model fit. Regression models applied to cost components (such as 'other treatments' and 'hospital costs') in the analyses above are also assumed to follow the same distributional assumptions as the total cost data. A standard ordinary least squares model

was also identified as the most appropriate model and applied to the analysis of incremental QALY gains. All analyses were conducted using heteroscedastic robust standard errors.

Non-parametric bootstrapping methods were used to estimate CIs to characterise uncertainty surrounding the point estimate of the ICER, using 1000 repetitions.⁴⁵ This uncertainty in the ICER is summarised using the following methods.

1. Incremental scatterplots of the 1000 replicates of joint differences in mean costs and QALYs for TH compared with SH compared with TH.⁴⁶ The incremental cost-effectiveness scatterplots allow one to see the probability of each intervention falling into each quadrant of the cost-effectiveness plane, being (1) less costly and more clinically effective; (2) more costly and less clinically effective; (3) less costly and less clinically effective; or (4) more costly and more clinically effective.
2. The bootstrapped estimates of joint differences in cost effects were further used to generate CEACs. CEACs were generated using estimates of net monetary benefit, generated using the bootstrapped replications, in accordance with the incremental net benefit (INB) statistic given in the following equation:

$$\text{INB} = \text{QALY} \times \lambda - \text{cost}. \quad (1)$$

This is calculated by multiplying the incremental effects (QALYs) by the decision-makers' WTP cost-effectiveness threshold [λ] and subtracting the incremental cost. Although the base-case analysis INB statistic was calculated based on the upper end of the threshold set by NICE (i.e. £30,000), several cost-per-QALY thresholds ranging from £0 to £50,000 are also reported. A positive INB suggests that the intervention is cost-effective versus its comparator at the defined threshold.

Deterministic sensitivity analyses

The presentation of CEACs and scatterplots addresses some of the sampling uncertainty in the data; however, other assumptions surrounding the most appropriate discount rate and analysis models undertaken may create additional uncertainty that is not captured in the presented CEACs. The impact of using MI to impute missing data was also explored by running a complete analysis (including only participants with complete cost and QALY data).

Subgroup analyses

Like the clinical analysis subgroup, analyses explored the possible treatment effect modification of clinically important factors (haemorrhoidal grade and sex) through the use of treatment by factor interaction. We did not identify any additional subgroup analyses that were required to estimate cost-effectiveness for the within-trial analysis.

Chapter 4 Participant baseline characteristics

Study recruitment

In total, 777 participants were recruited for surgical treatment from 29 out of the 32 UK-wide NHS hospitals that took part in the study (*Table 5*). Twenty-seven of these centres randomised 389 participants to the SH arm and 28 randomised 388 participants to the TH arm. Participants were recruited to the study between 13 January 2011 and 1 August 2014 and followed up to July 2016; however, not all the centres recruited within this period, owing to staggered introduction and early closure of centres. The trajectory of recruitment from all centres is shown in *Figure 2*.

Participant flow

Figure 3 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram for the study. In total, 1127 participants were screened and 1056 were found to be eligible. For the 279 excluded participants,

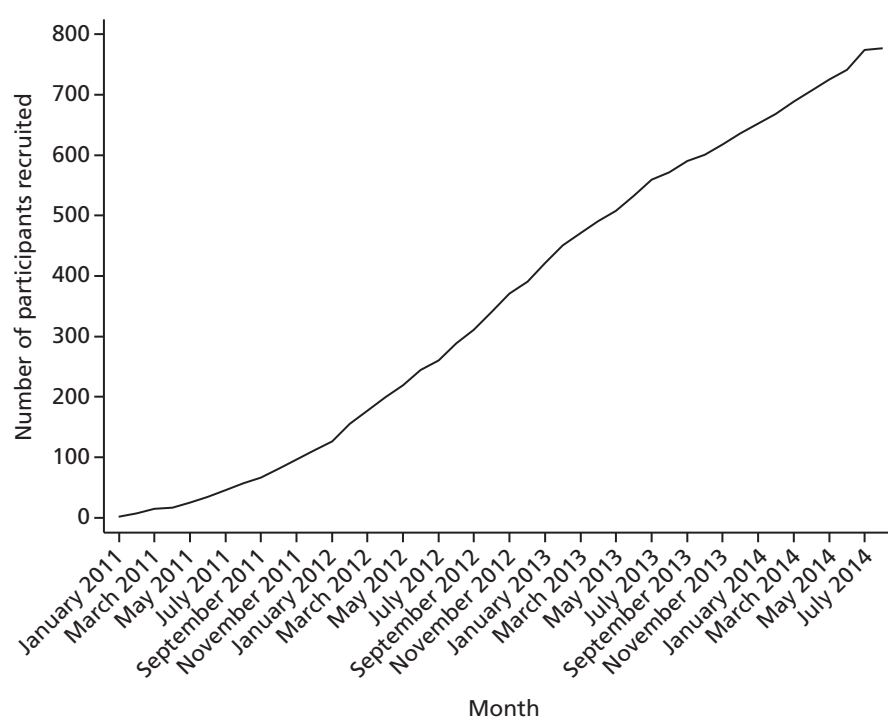
TABLE 5 Recruitment by centre

Hospital	Participants, n (%)					Randomised to receive	
	Eligible (N = 1056)	Excluded (N = 33)	Declined (N = 225)	Missed (N = 21)	Randomised (N = 777)	SH (N = 389)	TH (N = 388)
Aberdeen Royal Infirmary	176		17 (7.6)		159 (20.5)	79 (20.3)	80 (20.6)
Arrowe Park Hospital	4				4 (0.5)	1 (0.3)	3 (0.8)
Barnet General Hospital							
Basildon University Hospital							
Chelsea and Westminster Hospital	13	1(3.0)	6 (2.7)		6 (0.8)	3 (0.8)	3 (0.8)
Colchester University Hospital	16		13 (5.8)	1 (4.8)	2 (0.3)		2 (0.5)
Croydon University Hospital	74		14 (6.2)	1 (4.8)	59 (7.6)	30 (7.7)	29 (7.5)
Dr Gray's Hospital, Elgin	6		1 (0.4)		5 (0.6)	3 (0.8)	2 (0.5)
Forth Valley Royal Hospital	54		20 (8.9)		34 (4.4)	18 (4.6)	16 (4.1)
Glan Clwyd Hospital, Rhyl	19		6 (2.7)		13 (1.7)	7 (1.8)	6 (1.5)
Glasgow Southern General Hospital	1		1 (0.4)				
Hillingdon Hospital	49		12 (5.3)	4 (19.0)	33 (4.2)	16 (4.1)	17 (4.4)
Huddersfield Royal Infirmary	43		16 (7.1)	3 (14.3)	24 (3.1)	12 (3.1)	12 (3.1)
James Cook University Hospital	63		3 (1.3)	1 (4.8)	59 (7.6)	30 (7.7)	29 (7.5)
John Radcliffe Hospital	15		4 (1.8)		11 (1.4)	6 (1.5)	5 (1.3)
Lincoln County Hospital	12		1 (0.4)		11 (1.4)	6 (1.5)	5 (1.3)
Manchester Royal Infirmary	29	2(6.1)	11 (4.9)		16 (2.1)	8 (2.1)	8 (2.1)

continued

TABLE 5 Recruitment by centre (*continued*)

Hospital	Participants, <i>n</i> (%)					Randomised to receive	
	Eligible (<i>N</i> = 1056)	Excluded (<i>N</i> = 33)	Declined (<i>N</i> = 225)	Missed (<i>N</i> = 21)	Randomised (<i>N</i> = 777)	SH (<i>N</i> = 389)	TH (<i>N</i> = 388)
Nevill Hall Hospital	6		1 (0.4)	1 (4.8)	4 (0.5)	2 (0.5)	2 (0.5)
Norfolk and Norwich University Hospital	19		12 (5.3)	1 (4.8)	6 (0.8)	3 (0.8)	3 (0.8)
Northern General Hospital	25		13 (5.8)		12 (1.5)	6 (1.5)	6 (1.5)
Pinderfields Hospital	23		3 (1.3)		20 (2.6)	11 (2.8)	9 (2.3)
Queen Elizabeth Hospital	5				5 (0.6)	2 (0.5)	3 (0.8)
Raigmore Hospital	102	7 (21.2)	8 (3.6)		87 (11.2)	44 (11.3)	43 (11.1)
Royal Cornwall Hospital	32		17 (7.6)	4 (19.0)	11 (1.4)	6 (1.5)	5 (1.3)
Royal Derby City Hospital	35				35 (4.5)	18 (4.6)	17 (4.4)
Royal Sussex County Hospital	66				66 (8.5)	33 (8.5)	33 (8.5)
St James's Hospital	3			2 (9.5)	1 (0.1)	1 (0.3)	
University Hospital Aintree	7		5 (2.2)		2 (0.3)		2 (0.5)
University Hospital of North Durham	54		17 (7.6)		37 (4.8)	18 (4.6)	19 (4.9)
University Hospital of North Tees	56		9 (4.0)		47 (6.0)	23 (5.9)	24 (6.2)
Weston Hospital	3	1 (3.0)			2 (0.3)	1 (0.3)	1 (0.3)
Wythenshawe Hospital	46	22 (66.7)	15 (6.7)	3 (14.3)	6 (0.8)	2 (0.5)	4 (1.0)

**FIGURE 2** Recruitment over time.

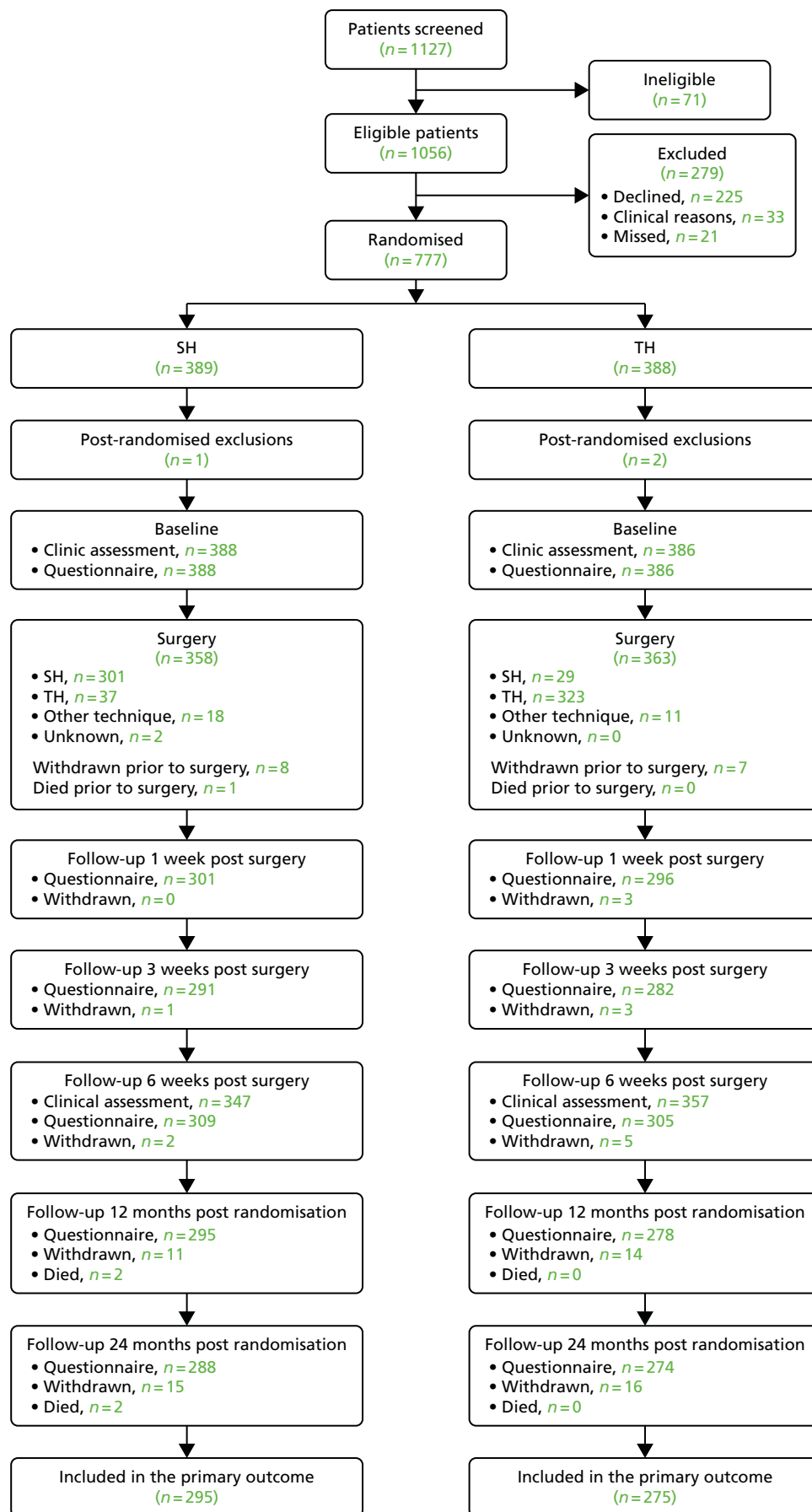


FIGURE 3 The CONSORT flow diagram.

225 declined, 33 were excluded because of clinical reasons and 21 were missed. The main reasons for ineligibility resulted from the participants having had previous surgery (26.8%) and being unable to complete study questionnaires (23.9%). The most frequent reasons for participants declining resulted from treatment preference (22.2%) and not wanting surgery (14.7%). Further details on reasons why screened participants were not randomised can be found in *Table 6*. Three participants were excluded post randomisation. One was under the age of 18 years and two withdrew consent within a short period following randomisation. Therefore, 774 participants were included in the study analysis and presentation of findings.

All the participants randomised attended the baseline clinical assessment and completed the baseline questionnaire. A total of 31 participants withdrew from the study; one withdrawal was caused by the surgeon's decision, whereas the remaining were at the participants' request. Details of the treatment received are described in *Chapter 5*. Six weeks post surgery, 704 participants attended clinical follow-up appointments and 614 responded to the questionnaire. At the 24-month post-randomisation follow-up, 562 participants responded; a total of 31 participants withdrew from the study by that time point. Two deaths were reported, and none was caused by a study intervention.

TABLE 6 Description of the ineligible participants

Reason	Number of participants, <i>n</i>	% of total number of participants excluded
Reasons for ineligibility (<i>n</i> = 71)		
Previous surgery	19	26.8
Sphincter injury	1	1.4
Inflammatory bowel disease	5	7.0
Malignant colorectal disease	2	2.8
Unable to complete	17	23.9
Other	27	38.0
Reasons for declining to take part (<i>n</i> = 225)		
Participant had a preference for treatment	50	22.2
Participant did not want to be randomised	16	7.1
Participant did not want to have surgery	33	14.7
Participant wanted to have a particular surgeon	5	2.2
Participant had concerns over their health	4	1.8
Participant not interested or did not want to take part in the study	4	1.8
Participant had no time to fill in questionnaires	3	1.3
Participant did not want any treatment	1	0.4
No reason given	109	48.4
Clinical reasons (<i>n</i> = 33)		
Surgeon felt that participant would benefit from a certain procedure	11	33.3
More than one procedure to be performed	22	66.7
Reasons for missing participants (<i>n</i> = 21)		
No response from the participant	12	57.1
Insufficient time to approach the participant	4	19.0
Participant received the information too late	2	9.5
Other	3	14.3

Baseline characteristics

The participants' baseline characteristics are shown for the 774 participants in *Table 7* (excluding the post-randomisation exclusions). Sex, grade of haemorrhoids and EQ-5D-3L score were included as minimisation variables; therefore, the balance between the two treatment groups for these covariates was ensured. The median age was 50 years old and the quality-of-life outcomes (SF-36; physical and mental component summary) were balanced between the groups. Over 60% of participants had grade-III haemorrhoids, and 35.8% of participants in the SH arm and 30.1% in the TH arm had had previous haemorrhoid treatment. The majority of participants had either no preference for the type of surgery or preferred an intervention associated with a lower risk of haemorrhoid recurrence.

Table 8 summarises the level of experience of the surgeons and is broken down by surgical procedure and not randomisation group. The number of SH and TH operations performed in the previous year per surgeon are similar, whereas the number performed during a surgeon's career differs.

TABLE 7 Baseline characteristics (participants)

Characteristic	Trial arm	
	SH (N = 388)	TH (N = 386)
Age (years), <i>n</i> , median (IQR)	388, 50 (40–60)	386, 49 (40–59)
Sex (male), <i>n</i> (%)	201 (51.8)	197 (51.0)
BMI (kg/m ²), <i>n</i> , mean (SD)	372, 27.0 (5.2)	367, 27.0 (4.9)
Grade of haemorrhoid, <i>n</i> (%)		
II	86 (22.2)	86 (22.3)
III	243 (62.6)	240 (62.2)
IV	59 (15.2)	60 (15.5)
Previous haemorrhoid surgery, <i>n</i> (%)	139 (35.8)	116 (30.1)
Comorbidities, <i>n</i> (%)	6 (1.5)	4 (1.0)
Systemic medications, <i>n</i> (%)		
Aspirin	23 (5.9)	16 (4.1)
Warfarin	4 (1.0)	2 (0.5)
Clopidogrel	6 (1.5)	4 (1.0)
Steroids	5 (1.3)	2 (0.5)
Immunosuppressants	1 (0.3)	
Other	6 (1.5)	3 (0.8)
Pain (VAS), <i>n</i> , mean (SD)	379, 2.8 (2.7)	383, 2.5 (2.6)
Analgesia, <i>n</i> (%)		
Yes	139 (35.8)	118 (30.6)
Missing	7 (1.8)	4 (1.0)
Number of days in a week with analgesia, <i>n</i> , mean (SD)	137, 4.1 (2.2)	117, 4.3 (2.2)
EQ-5D-3L, <i>n</i> , mean (SD)	388, 0.764 (0.264)	386, 0.762 (0.246)

continued

TABLE 7 Baseline characteristics (participants) (*continued*)

Characteristic	Trial arm	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
SF-36, <i>n</i> , mean (SD)		
Physical component summary	380, 48.5 (9.4)	377, 48.8 (9.5)
Mental component summary	380, 48.8 (11.7)	377, 49.6 (11.0)
CIS, <i>n</i> , mean (SD)	376, 4.3 (3.9)	376, 4.1 (4.0)
HSS, <i>n</i> , mean (SD)	370, 10.8 (4.7)	370, 10.4 (4.7)
Patient reporting tenesmus, <i>n</i> (%)		
Always	15 (3.9)	9 (2.3)
Often	52 (13.4)	39 (10.1)
Sometimes	93 (24.0)	105 (27.2)
Rarely	73 (18.8)	62 (16.1)
Never	150 (38.7)	168 (43.5)
Missing	5 (1.3)	3 (0.8)
Patient preference, <i>n</i> (%)		
Strongly prefer better short-term recovery	23 (5.9)	38 (9.8)
Prefer better short-term recovery	35 (9.0)	24 (6.2)
No preference	161 (41.5)	146 (37.8)
Prefer lower risk of recurrence	95 (24.5)	85 (22.0)
Strongly prefer lower risk of recurrence	68 (17.5)	91 (23.6)
Missing	6 (1.5)	2 (0.5)
BMI, body mass index.		

TABLE 8 Baseline characteristics (surgeons)

Characteristic	Trial arm	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
Number of operations performed during career		
<i>n</i> , mean (SD)	42, 102.7 (98.9)	42, 200.1 (232.3)
Median (IQR)	85 (30.0–115.0)	100 (70.0–200.0)
Operations performed in previous year		
<i>n</i> , mean (SD)	43, 12.9 (10.3)	40, 14.7 (12.6)
Median (IQR)	10 (4.0–21.0)	10 (4.5–23.0)

Chapter 5 Outcomes and results

Description of sample

The surgical procedures received by each treatment group are shown in *Table 9*. Of the 388 participants randomised to receive SH, 358 (92.3%) had surgery and, of these, 301 (84.1%) received their allocated intervention, 37 (10.3%) received TH, 18 (5.0%) had a technique other than the study interventions and two (0.6%) are unknown as they underwent private treatment. For the 386 participants randomised to receive TH, 363 (94.0%) had surgery, 323 (89.0%) received their allocated treatment, 29 (8.0%) received SH and 11 (3.0%) received other treatments. Across both arms 53 (6.8%) participants did not receive surgery, and the reasons are shown in *Table 10*.

Surgical details

For the SH procedure, the most common staplers used were the Ethicon and the Chex staplers, used on 177 (53.6%) and 123 (37.3%) patients, respectively. For the TH procedure, the Milligan–Morgan approach was the main surgical approach, performed on 308 (85.6%) patients. The majority of participants were operated on by consultant surgeons (71.5% in the SH arm and 62.0% in the TH arm). Specialty doctors performed 8.9% of operations in the SH arm and 10.2% in the TH arm and surgical trainees performed 16.2% of the SH surgeries and 24.5% of the TH surgeries. Most procedures were performed either under general anaesthesia (65.9% in the SH arm and 61.4% in the TH arm) or with an additional local anaesthetic block in 29.3% of the SH arm and 35.0% of the TH arm. The mean duration of the operation was the same in both groups (0.4 hours), 305 (85.6%) in the SH arm and 317 (87.3%) in the TH arm were day cases and the mean number of days to surgery was similar for both groups (68.2 days in the SH arm and 68.8 days in the TH arm).

TABLE 9 Surgical procedure

Surgery details	Trial arm	
	SH (N = 388)	TH (N = 386)
Received surgery, n (%)		
Yes	358 (92.3)	363 (94.0)
No	30 (7.7)	23 (6.0)
Surgical technique, n (%)		
Stapling	301 (84.1)	29 (8.0)
Ethicon	155 (51.5)	22 (75.9)
Chex CPH 32 staple gun	117 (38.9)	6 (20.7)
EEA Staplers with DST Series technology	9 (3.0)	–
Other	10 (3.3)	1 (3.4)
Missing	10 (3.3)	–

continued

TABLE 9 Surgical procedure (continued)

Surgery details	Trial arm	
	SH (N = 388)	TH (N = 386)
Traditional	37 (10.3)	323 (89.0)
Open (Milligan–Morgan)	36 (97.3)	272 (84.2)
Closed (Ferguson)	1 (2.7)	41 (12.7)
Other conventional technique	–	5 (1.5)
Missing	–	5 (1.5)
Other technique	18 (5.0)	11 (3.0)
Surgery technique unknown	2 (0.6)	–
Surgeon grade, n (%)		
Consultant	256 (71.5)	225 (62.0)
Specialty doctor	32 (8.9)	37 (10.2)
Surgical trainee	58 (16.2)	89 (24.5)
Fellow	4 (1.1)	5 (1.4)
Other	5 (1.4)	6 (1.7)
Missing	3 (0.8)	1 (0.3)
Anaesthetist present, n (%)		
Yes	356 (99.4)	363 (100.0)
Missing	2 (0.6)	–
Anaesthetist grade, n (%)		
Consultant	287 (80.2)	297 (81.8)
Specialty doctor	45 (12.6)	36 (9.9)
Fellow	–	1 (0.3)
Registrar	10 (2.8)	21 (5.8)
Other	2 (0.6)	–
Missing	14 (3.9)	8 (2.2)
Type of anaesthesia, n (%)		
General	236 (65.9)	223 (61.4)
General and local anaesthetic block	105 (29.3)	127 (35.0)
Spinal	15 (4.2)	11 (3.0)
Other	–	1 (0.3)
Missing	2 (0.6)	1 (0.3)
Duration of operation (hours), n, mean (SD)	346, 0.4 (0.2)	359, 0.4 (0.2)
Length of hospital stay (days), n, mean (SD)	356, 0.4 (0.3)	363, 0.4 (0.4)
Day cases, n (%)	305 (85.6)	317 (87.3)
Time from randomisation to surgery (days), n, mean (SD)	358, 68.2 (78.3)	363, 68.8 (81.1)

TABLE 10 Reasons for not having surgery

Reason	Number of participants, <i>n</i> (%) (<i>N</i> = 53)
Patient reasons	39 (73.6)
Opted out of surgery	15
Cancelled surgery	10
Did not attend	7
Went private	3
Moved away	2
Withdrew prior to surgery (withdrew outcome data)	1
Withdrew consent	1
Clinical reasons	10 (18.9)
Underlying health condition	5
Following preoperative consultation conservative management was decided	1
Pregnancy	1
Following preoperative consultation did not require surgery	3
Unknown	3 (5.7)
Death prior to surgery	1 (1.9)

Primary outcome

The EQ-5D-3L values at each time point are shown in *Table 11*. *Figure 4* shows the profile for the two treatment groups over the study period, whereas *Figure 5* shows the profile for the earlier follow-up time points. The SH arm had higher EQ-5D-3L scores for 1 week and 3 weeks, but this changed to higher scores in the TH arm from 6 weeks onwards. The primary outcome, EQ-5D-3L AUC over 24 months post randomisation, reported as QALYs (*Table 12*), favoured TH (−0.073 QALYs, 95% CI −0.140 to −0.006 QALYs; $p = 0.034$). The secondary analysis of AUC over 6 weeks post surgery favoured SH and the AUC over 12 months post randomisation showed no evidence of a difference between the two interventions. The analyses restricted to participants with at least one long-term measure were similar, and exploring the sensitivities to assumptions (per-protocol and MI analyses) gave similar results (*Tables 13–16*).

TABLE 11 Participant EQ-5D-3L scores at each time point

Time point	Trial arm, <i>n</i> , mean (SD)	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
Baseline	388, 0.762 (0.247)	386, 0.764 (0.264)
1 week	298, 0.592 (0.315)	291, 0.458 (0.337)
3 weeks	285, 0.802 (0.244)	276, 0.750 (0.244)
6 weeks	305, 0.843 (0.226)	303, 0.853 (0.228)
12 months	296, 0.816 (0.258)	280, 0.877 (0.212)
24 months	283, 0.830 (0.251)	272, 0.872 (0.195)

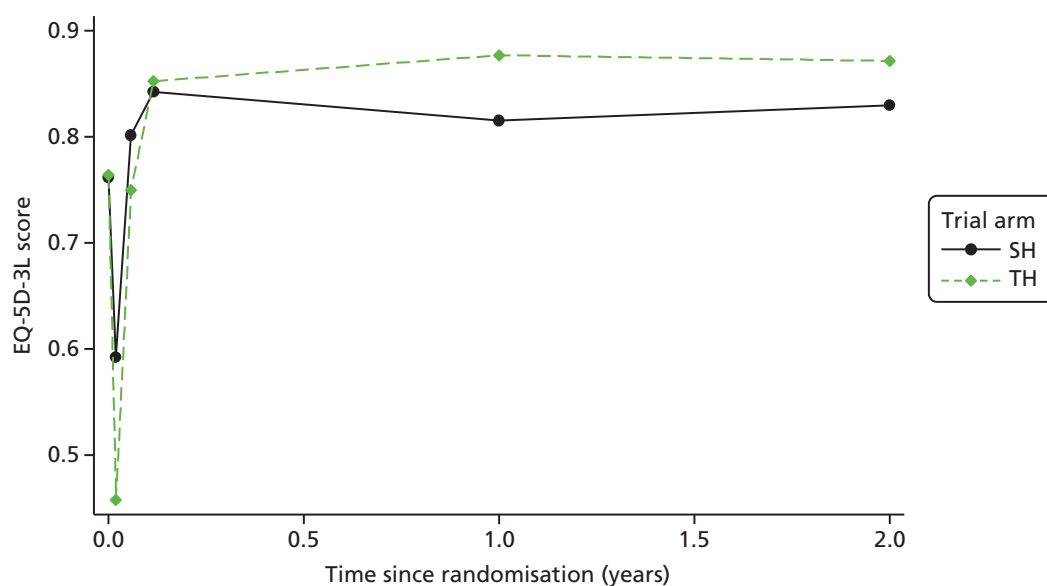


FIGURE 4 Participant EQ-5D-3L scores up to 2 years. Participants need to have at least one short-term and one long-term follow-up score over 2 years.

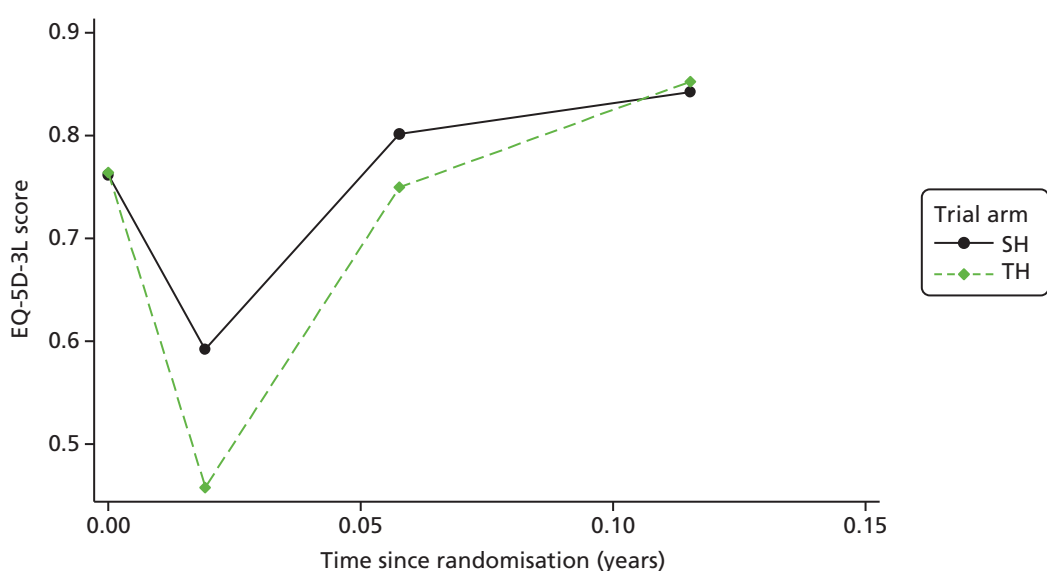


FIGURE 5 Participant EQ-5D-3L scores up to 6 weeks. Participants need to have at least one short-term follow-up score over 6 weeks.

TABLE 12 Primary outcome: EQ-5D-3L AUC (QALYs)^a

Time point	Trial arm, n, mean AUC (SD)		MD (95% CI)	p-value
	SH (N = 388)	TH (N = 386)		
6 weeks	331, 0.215 (0.150)	328, 0.197 (0.143)	0.020 (0.003 to 0.038)	0.024
12 months	282, 0.824 (0.218)	262, 0.828 (0.225)	-0.010 (-0.039 to 0.019)	0.483
24 months	295, 1.556 (0.483)	275, 1.618 (0.431)	-0.073 (-0.140 to -0.006)	0.034

MD, mean difference.

^a Participants need to have at least one short-term and one long-term follow-up score at 12 and 24 months, and one short-term follow-up score at 6 weeks.

TABLE 13 Primary outcome: EQ-5D-3L AUC (QALYs)^a

Time point	Trial arm, <i>n</i> , mean AUC (SD)		MD (95% CI)	<i>p</i> -value
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)		
12 months	29, 0.821 (0.219)	280, 0.828 (0.225)	−0.015 (−0.040 to 0.011)	0.249
24 months	315, 1.541 (0.489)	294, 1.609 (0.435)	−0.077 (−0.137 to −0.017)	0.013

MD, mean difference.
a Participants with at least one long-term follow-up score.

TABLE 14 Primary outcome: EQ-5D-3L AUC (QALY)^a

Time point	Trial arm, <i>n</i> , mean AUC (SD)		MD (95% CI)	<i>p</i> -value
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)		
6 weeks	282, 0.225 (0.151)	299, 0.197 (0.142)	0.029 (0.010 to 0.048)	0.004
12 months	240, 0.823 (0.217)	243, 0.827 (0.219)	−0.009 (−0.040 to 0.022)	0.565
24 months	251, 1.555 (0.478)	256, 1.623 (0.418)	−0.078 (−0.153 to −0.002)	0.045

MD, mean difference.
a Participants need to have at least one short- and one long-term follow-up score per protocol.

TABLE 15 Primary outcome: AUC EQ-5D-3L (QALY)^a

Time point	Trial arm, <i>n</i> , mean AUC (SD)		MD (95% CI)	<i>p</i> -value
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)		
12 months	247, 0.824 (0.215)	246, 0.828 (0.219)	−0.011 (−0.041 to 0.020)	0.467
24 months	258, 1.550 (0.479)	260, 1.616 (0.429)	−0.078 (−0.152 to −0.004)	0.039

MD, mean difference.
a Participants with at least one long-term follow-up score per protocol.

TABLE 16 The AUC EQ-5D-3L (QALYs)^a

	Trial arm, <i>n</i>			
Time point	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)	MD (95% CI)	<i>p</i> -value
<i>Participants who either had surgery or at least one follow-up</i>				
6 weeks	354	358	0.024 (0.004 to 0.043)	0.020
12 months	360	367	−0.012 (−0.038 to 0.014)	0.350
24 months	363	369	−0.063 (−0.111 to −0.015)	0.013
<i>All participants randomised</i>				
6 weeks	388	386	0.020 (−0.002 to 0.042)	0.071
12 months	388	386	−0.007 (−0.345 to 0.018)	0.571
24 months	388	386	−0.054 (−0.107 to −0.000)	0.049
MD, mean difference. a MI.				

Secondary outcomes

Quality of life

The SF-36 mental and physical component summary scores, CIS and HSS are shown in *Table 17*. Six weeks after surgical intervention, the physical and mental components scores were either similar to, or less than, the baseline scores, and there was no evidence of a difference between the two interventions. At 12 and 24 months after randomisation both scores improved, and there is evidence of a difference in favour of TH at 12 months [physical summary: mean difference (MD) -1.79 , 95% CI -3.06 to -0.51 , $p = 0.006$; mental summary: MD -1.71 , 95% CI -3.34 to -0.08 , $p = 0.040$].

The CIS at 6 weeks was similar for both groups [SH arm: 5.1 (SD 4.5); TH arm: 5.0 (SD 4.3)], but at 12 and 24 months post randomisation there is evidence of a difference between the two groups (12 months: MD 1.20, 95% CI 0.58 to 1.81, $p < 0.001$; 24 months: MD 0.78, 95% CI 0.15 to 1.42, $p = 0.015$). The HSS favours TH over SH at all time points (6 weeks: MD 0.15, 95% CI -0.60 to 0.91, $p = 0.691$; 12 months: MD 2.09, 95% CI 1.28 to 2.90, $p < 0.001$; 24 months: MD 1.46, 95% CI 0.64 to 2.28, $p < 0.001$).

TABLE 17 Quality of life

	Trial arm, <i>n</i> , mean score (SD)			
Time point	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)	MD (95% CI)	<i>p</i> -value
SF-36				
<i>Physical component summary</i>				
Baseline	380, 48.5 (9.4)	377, 48.8 (9.5)	–	–
6 weeks	294, 48.2 (10.4)	293, 48.9 (9.2)	–0.58 (–1.77 to 0.61)	0.342
12 months	265, 49.7 (10.1)	255, 51.2 (9.4)	–1.79 (–3.06 to –0.51)	0.006
24 months	250, 50.3 (10.1)	234, 51.1 (9.4)	–1.15 (–2.47 to 0.16)	0.086
<i>Mental component summary</i>				
Baseline	380, 48.8 (11.7)	377, 49.6 (11.0)	–	–
6 weeks	294, 47.3 (12.7)	293, 48.7 (11.7)	–0.55 (–2.07 to 0.97)	0.480
12 months	265, 48.8 (12.2)	255, 51.2 (10.4)	–1.71 (–3.34 to –0.08)	0.040
24 months	250, 49.8 (11.2)	234, 51.0 (10.9)	–0.89 (–2.57 to 0.80)	0.303
CIS				
Baseline	376, 4.3 (3.9)	376, 4.1 (4.0)	–	–
6 weeks	288, 5.1 (4.5)	290, 5.0 (4.3)	–0.16 (–0.74 to 0.42)	0.584
12 months	266, 4.4 (4.3)	247, 2.9 (3.5)	1.20 (0.58 to 1.81)	< 0.001
24 months	249, 3.8 (3.8)	235, 3.0 (3.4)	0.78 (0.15 to 1.42)	0.015
HSS				
Baseline	370, 10.8 (4.7)	370, 10.4 (4.7)	–	–
6 weeks	288, 8.2 (5.1)	291, 7.9 (5.0)	0.15 (–0.60 to 0.91)	0.691
12 months	263, 6.6 (5.1)	243, 4.3 (4.3)	2.09 (1.28 to 2.90)	< 0.001
24 months	250, 6.4 (5.0)	240, 4.8 (4.4)	1.46 (0.64 to 2.28)	< 0.001
MD, mean difference.				

Patient-reported pain measures

There is evidence that pain, recorded on the VAS, was lower in the SH arm than in the TH arm at both 1 week (MD -1.35 , 95% CI -1.81 to -0.89 ; $p < 0.001$) and 3 weeks after surgery (MD -0.72 , 95% CI -1.16 to -0.028 ; $p = 0.003$). The number of days with analgesia was significantly different and in favour of SH at 1 week (MD -0.59 , 95% CI -0.98 to -0.20 ; $p = 0.004$), but not at 3 weeks. Pain scores and the number of days with analgesia at 6 weeks showed no difference between the arms and the proportion of participants returning to usual activities was the same (89%). Results are shown in *Table 18*.

Participant-reported recurrence

At 12 months post randomisation more participants in the SH arm reported that their haemorrhoids had recurred ($n = 94$, 31.9%) than in the TH arm ($n = 39$, 14.0%) [odds ratio (OR) 2.96, 95% CI 2.02 to 4.32; $p < 0.001$]. This was also the case at 24 months; 134 (42.3%) reoccurrences were reported in the SH arm compared with 76 (25.3%) in the TH arm (*Table 19*).

Tenesmus

Table 20 shows that tenesmus at 6 weeks post surgery, and 12 and 24 months post randomisation was more prevalent in the SH arm.

Further haemorrhoid surgery

In total, 34 (9.3%) participants in the SH arm had to have further surgery compared with 23 (6.2%) in the TH arm ($p = 0.111$; *Table 21*).

TABLE 18 Pain, analgesia and return to usual activities

Time point	Trial arm		Effect size ^b (95% CI)	<i>p</i> -value
	SH (<i>N</i> = 388) ^a	TH (<i>N</i> = 386) ^a		
Pain at 1 week post surgery				
Number of patients followed up, <i>n</i> (%)	301 (77.6)	296 (76.7)	–	–
Worst pain (VAS)	298, 6.9 (2.5)	295, 7.9 (2.2)	–1.04 (–1.59 to –0.49)	0.001
Pain (VAS)	299, 4.0 (2.5)	296, 5.3 (2.6)	–1.35 (–1.81 to –0.89)	< 0.001
Analgesia, <i>n</i> (%)	285 (94.7)	286 (96.6)	0.57 (0.27 to 1.19)	0.134
Number of days with analgesia	285, 5.8 (1.7)	286, 6.4 (1.3)	–0.59 (–0.98 to –0.20)	0.004
Pain at 3 weeks post surgery				
Number of patients followed up, <i>n</i> (%)	291 (75.0)	282 (73.1)	–	–
Pain (VAS)	290, 1.8 (2.2)	281, 2.6 (2.5)	–0.72 (–1.16 to –0.28)	0.003
Analgesia, <i>n</i> (%)	111 (38.1)	145 (51.4)	0.58 (0.45 to 0.75)	< 0.001
Number of days with analgesia	111, 4.3 (2.1)	145, 4.5 (2.2)	–0.24 (–0.75 to 0.27)	0.340
Pain at 6 weeks post surgery				
Number of patients followed up, <i>n</i> (%)	309 (79.6)	305 (79.0)	–	–
Pain (VAS)	304, 1.3 (2.0)	301, 1.3 (1.9)	–0.01 (–0.35 to 0.33)	0.961
Analgesia, <i>n</i> (%)	73 (23.6)	67 (22.0)	1.11 (0.73 to 1.68)	0.620
Number of days in a week with analgesia	72, 4.7 (2.3)	67, 4.0 (2.3)	0.58 (–0.22 to 1.37)	0.146
Returned to usual activities after 6 weeks, <i>n</i> (%)	276 (89.3)	271 (88.9)	1.05 (0.64 to 1.71)	0.854

^a Value are n , mean (SD) unless stated otherwise.

^b Effect sizes are mean difference apart from analgesia, which is reported as ORs.

TABLE 19 Participant-reported recurrence

Time point	Trial arm, <i>n</i> (%)		OR ^a (95% CI)	<i>p</i> -value
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)		
12 months post randomisation				
Participants followed up	295	278	–	–
Haemorrhoids reoccurred	94 (31.9)	39 (14.0)	2.96 (2.02 to 4.32)	< 0.001
24 months post randomisation				
Participants followed up	317	300	–	–
Haemorrhoids reoccurred	134 (42.3)	76 (25.3)	2.25 (1.46 to 3.46)	< 0.001

TABLE 20 Tenesmus

	Trial arm, <i>n</i> (%)		
Time point	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)	<i>p</i> -value
6 weeks			
Participants followed up	309	305	0.001
Always	17 (5.5)	9 (3.0)	
Often	42 (13.6)	20 (6.6)	
Sometimes	82 (26.5)	75 (24.6)	
Rarely	58 (18.8)	68 (22.3)	
Never	109 (35.3)	131 (43.0)	
Missing	1 (0.3)	2 (0.7)	
12 months			
Participants followed up	295	278	< 0.001
Always	11 (3.7)	4 (1.4)	
Often	27 (9.2)	7 (2.5)	
Sometimes	60 (20.3)	46 (16.5)	
Rarely	65 (22.0)	43 (15.5)	
Never	113 (38.3)	154 (55.4)	
Missing	19 (6.4)	24 (8.6)	
24 months			
Participants followed up	288	274	0.001
Always	6 (2.1)	3 (1.1)	
Often	27 (9.4)	13 (4.7)	
Sometimes	51 (17.7)	36 (13.1)	
Rarely	55 (19.1)	47 (17.2)	
Never	119 (41.3)	143 (52.2)	
Missing	30 (10.4)	32 (11.7)	

TABLE 21 Further surgical interventions

Time point	Trial arm, <i>n</i> (%)						<i>p</i> -value
	SH (<i>N</i> = 388)			TH (<i>N</i> = 386)			
Participant	Registry ^a	Combined ^b	Participant	Registry ^a	Combined ^b		
Participants followed up at 6 weeks	348	343	348	356	354	357	
Within 6 weeks of surgery							
TH	1 (0.3)	–	1 (0.3)	–	–	–	–
RBL	–	–	–	–	1 (0.3)	1 (0.3)	
At 6 weeks							
TH	6 (1.7)	–	6 (1.7)	2 (0.6)	–	2 (0.6)	–
SH	3 (0.9)	–	3 (0.9)	1 (0.3)	–	1 (0.3)	
RBL	4 (1.1)	–	4 (1.1)	6 (1.7)	–	6 (1.7)	
Skin tags	5 (1.4)	–	5 (1.4)	4 (1.1)	–	4 (1.1)	
Type of haemorrhoid surgery unknown	1 (0.3)	–	1 (0.3)	–			
12 months post randomisation							
Participants followed up at 12 months	288	374	299	272	379	283	–
TH	6 (2.1)	5 (1.3)	11 (3.7)	–	3 (0.8)	3 (1.1)	
SH	–	1 (0.3)	1 (0.3)	–	1 (0.3)	1 (0.4)	
RBL	3 (1.0)	–	3 (1.0)	3 (1.1)	2 (0.5)	5 (1.8)	
Skin tags	1 (0.3)	5 (1.3)	6 (2.0)	2 (0.7)	4 (1.1)	6 (2.1)	
24 months post randomisation							
Participants followed up at 24 months	286	374	289	273	379	274	
TH	2 (0.7)	–	2 (0.7)	1 (0.4)	–	1 (0.4)	
SH	2 (0.7)	2 (0.5)	4 (1.4)	–	–	–	
RBL	2 (0.7)	–	2 (0.7)	1 (0.4)	–	1 (0.4)	
Skin tags	–	1 (0.3)	1 (0.3)	–	1 (0.3)	1 (0.4)	
Type of haemorrhoid surgery unknown	1 (0.3)	–	1(0.3)	1 (0.4)	–	1 (0.4)	
Number of participants who had further surgical treatment	–	–	34/364 (9.3)	–	–	23/371 (6.2)	0.111

^a Registry = HES, PEDW and ISD.

^b Combined = participant + HES, PEDW and ISD.

Further interventions: non-surgical

In total, 94 (25.8%) participants in the SH arm had to have further non-surgical interventions compared with 70 (18.9%) in the TH arm (*Table 22*). This included patients who had received intramuscular onabotulinumtoxinA (Botox®; Allergan, Marlow, UK) injections and other medical treatments.

Perioperative and postoperative complications

The number of participants who had complications before discharge was similar in both groups [18 (5.0%) in the SH arm; 19 (5.2%) in the TH arm; $p = 0.9$], but after discharge there were slightly more in the TH arm [96 (24.9%) in the SH arm; 117 (30.6%) in the TH arm; OR 0.75, 95% CI 0.57 to 0.98; $p = 0.034$] (*Table 23*). Further details of the other complications (perioperative, post operative and within 6 weeks) are given in *Tables 24* and *25*, and details of the complications at 12 and 24 months post randomisation are given in *Table 26*.

TABLE 22 Further non-surgical interventions

Time point	Trial arm, n (%)					
	SH (N = 388)			TH (N = 386)		
	Participant	Registry ^a	Combined ^b	Participant	Registry ^a	Combined ^b
Participants followed up at 6 weeks	348	343	348	356	354	356
Within 6 weeks of surgery						
Botox	1 (0.3)	–	1 (0.3)	–	–	–
Medical treatment	11 (3.2)	–	11 (3.2)	16 (4.5)	–	16 (4.5)
At 6 weeks ^c						
Medical treatment	33 (9.5)	–	33 (9.5)	33 (9.3)	–	33 (9.3)
12 months post randomisation						
Participants followed up	288	374	288	272	379	272
Botox	1 (0.3)	–	1 (0.3)	–	1 (0.3)	–
Medical treatment	53 (18.4)	2(0.5)	53 (18.4)	31 (11.4)	2 (0.5)	31 (11.4)
24 months post randomisation						
Participants followed up	286	374	286	273	379	273
Botox	1 (0.3)	–	1 (0.3)	–	–	–
Medical treatment	38 (13.3)	–	38 (13.3)	19 (7.0)	–	19 (7.0)
Number of participants who had further non-surgical treatment	–	–	94/364 (25.8)	–	–	70/371 (18.9)
^a Registry = HES, PEDW and ISD. ^b Combined = participant + HES, PEDW and ISD. ^c Need for further treatment at the 6-week clinical appointment.						

TABLE 23 Complications

Complication	Trial arm, <i>n</i> (%)						OR (95% CI)	<i>p</i> -value
	SH (<i>N</i> = 388)			TH (<i>N</i> = 386)				
	Participant	Registry ^a	Combined ^b	Participant	Registry ^a	Combined ^b		
Participants who received surgery	358	–	358	363	–	363		
Perioperative complication								
Anaesthetic	1 (0.3)	–	1 (0.3)	2 (0.6)	–	2 (0.6)	–	–
Bleeding	6 (1.7)	–	6 (1.7)	6 (1.7)	–	6 (1.7)	–	
Other	4 (1.1)	–	4 (1.1)		–		–	
Postoperative complications prior to discharge								
Bleeding	1 (0.3)	–	1 (0.3)	1 (0.3)	–	1 (0.3)	–	
Need for blood transfusion	–	–	–	1 (0.3)	–	1 (0.3)	–	
Urinary retention	–	–	–	3 (0.8)	–	3 (0.8)	–	
Other	7 (2.0)	–	7 (2.0)	8 (2.2)	–	8 (2.2)	–	
Number of participants with a complication before discharge	–	–	–	18 (5.0)	–	19 (5.2)	–	0.900
Complications since discharge (at 6 weeks)								
Number of patients followed up	348	374	349	357	379	358	–	
Residual haemorrhoidal tissue	36 (10.3)	–	36 (10.3)	37 (10.4)	–	37 (10.3)	–	
Surgery for complications	7 (2.0)	2(0.5)	8 (2.3)	7 (2.0)	4 (1.1)	10 (2.8)	–	
Anal stenosis	6 (1.7)	–	6 (1.7)	2 (0.6)	–	2 (0.6)	–	
Anal fistula	2 (0.6)	–	2 (0.6)	2 (0.6)	–	2 (0.6)	–	
Anal fissure	11 (3.2)	–	11 (3.2)	13 (3.6)	–	13 (3.6)	–	
Wound discharge	6 (1.7)	–	6 (1.7)	27 (7.6)	–	27 (7.5)	–	

continued

continued

TABLE 23 Complications (*continued*)

Complication	Trial arm, <i>n</i> (%)						OR (95% CI)	<i>p</i> -value
	SH (<i>N</i> = 388)			TH (<i>N</i> = 386)				
	Participant	Registry ^a	Combined ^b	Participant	Registry ^a	Combined ^b		
Pelvic sepsis	–	–	–	2 (0.6)	–	2 (0.6)	–	
Need for blood transfusion	2 (0.6)	1 (0.3)	2 (0.6)	2 (0.6)	–	2 (0.6)	–	
Urinary retention requiring catheterisation	9 (2.6)	–	9 (2.6)	8 (2.2)	–	8 (2.2)	–	
Other	31 (8.9)	1 (0.3)	31 (8.9)	42 (11.8)	–	39 (10.9)	–	
Further surgery required for complications at 6 weeks	8 (2.3)	–	8 (2.3)	3 (0.8)	–	3 (0.8)	–	
Responded at 12 months and received surgery	295	374	295	278	379	278	–	
Complications	8 (2.7)	4 (1.1)	9 (3.1)	8 (2.9)	2 (0.5)	8 (2.9)	–	
Complications requiring surgery	3 (1.0)	6 (1.6)	8 (2.7)	1 (0.4)	1 (0.3)	1 (0.4)	–	
Responded at 24 months and received surgery	288	374	288	274	379	275	–	
Complications	3 (1.0)	2 (0.5)	3 (1.0)	–	1 (0.3)	1 (0.4)	–	
Complications requiring surgery	1 (0.3)	2 (0.5)	2 (0.7)	–	–	–	–	
Number of participants with a complication after discharge	–	–	96 (24.9)	–	–	117 (30.6)	0.75 (0.57 to 0.98)	0.034

^a Registry = HES, PEDW and ISD.

^b Combined = participant + HES, PEDW and ISD.

TABLE 24 Details of other complications: perioperative and post operative

Complication	Trial arm, <i>n</i>	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
Perioperative complication	4	–
Haematoma	1	–
Low staple line	1	–
Purse string snapped and redone	2	–
Postoperative complications prior to discharge	7	8
Pain	5	4
Anaesthetic	1	3
Urinary retention	–	1
Not specified	1	–

TABLE 25 Details of other postoperative complications at 6 weeks' clinical assessment (participant-reported and registry data)

Complication	Trial arm, <i>n</i>	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
Other complications	31	39
Pain	6	11
Bleeding	7	3
Pain and bleeding	1	6
Constipation	–	4
Pain and constipation	–	2
Bleeding and constipation	1	1
Faecal urgency	3	2
Incontinence	2	–
Infection	4	7
Other	7	3
Surgery within 6 weeks for complications	8	10
Pain	1	3
Pain and bleeding	1	–
Infection	1	–
Other	5	7
Further surgery required for complications at 6 weeks	8	3
Pain	–	1
Bleeding	1	–
Fissure	1	–
Other	6	2

TABLE 26 Details of other complications at 12 and 24 months post randomisation (participant-reported and registry data)

Complication	Trial arm, <i>n</i>	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
Complications at 12 months	9	8
Bleeding	4	2
Pain	–	1
Anal fissure	2	3
Urinary retention	1	1
Other	2	1
Surgery within 12 months for complications	8	1
Pain	1	1
Stricture	2	–
Anal fissure	2	–
Other	3	–
Complications at 24 months	3	1
Bleeding	1	–
Anal fissure	1	1
Other	1	–
Surgery within 24 months for complications	2	0
Stricture	1	–
Anal fissure	–	–
Other	1	–

Adverse events

In total, there were 61 SAEs during the study; 59 participants [28 (7.2%) in the SH arm and 31 (8.0%) in the TH arm] had an event (*Table 27*). *Table 28* gives details by randomisation group and *Table 29* by the treatment received. There were two deaths in the SH arm, both unrelated to haemorrhoid surgery. One patient died while abroad 1 year after surgery, with the cause unknown; the other participant was randomised to receive SH but did not receive surgery, and the cause of death was ketoacidosis. The majority of SAEs by treatment received were related to pain (six in the SH arm and 10 in the TH arm), bleeding (six in the SH arm and one in the TH arm) and participants requiring catheterisation for urinary retention (seven in the SH arm and four in the TH arm). Two participants in each surgery arm had two episodes of pain, two required a blood transfusion; one had a low haemoglobin concentration prior to surgery and the other was readmitted 1 week post surgery with severe postoperative bleeding, which required extensive hospital stay. A combination of pain, constipation and bleeding occurred in a small number of participants, and one participant who received SH and two who received TH had pain caused by fissure.

TABLE 27 Serious adverse events

SAE	Trial arm	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
Participants who had a SAE, <i>n</i> (%)	28 (7.2)	31 (8.0)
Total number of SAEs	29	32
Participant died, ^a <i>n</i>	2	–
Hospitalisation, <i>n</i>	18	17
Prolongation, <i>n</i>	7	13
Medically significant, <i>n</i>	1	2
Expected, ^b <i>n</i>	26	31
a Both deaths were unrelated to the study. b The two unexpected SAEs are the two deaths.		

TABLE 28 Details of the SAEs, by randomised group

SAE	Trial arm, <i>n</i>	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)
Death (unrelated to the study)	2	–
Infection	1	–
Urinary retention	3	8
Difficulty passing urine	2	–
Pain ^a	6	10
Pain and bleeding	1	1
Pain and stenosis	1	–
Stenosis	1	–
Pain caused by fissure	1	2
Constipation and urinary retention	–	2
Bleeding	7	–
Constipation	–	3
Pain and constipation	–	1
Constipation and bleeding	1	1
Pain, constipation and bleeding	–	1
Anaesthesia	–	2
Haemorrhoid symptoms	1	–
Fissure	1	–
a One participant in each group experienced two SAEs of pain.		

TABLE 29 SAEs with details by treatment received

SAE	Trial arm	
	SH (<i>N</i> = 388)	TH (<i>N</i> = 352)
Participants who had a SAE, <i>n</i> (%)	25 (7.6)	33 (9.2)
Total number of SAEs	26	34
Death (unrelated to the study), <i>n</i>	1	–
Infection, <i>n</i>	–	1
Urinary retention, <i>n</i>	4	7
Difficulty passing urine, <i>n</i>	2	–
Pain, ^a <i>n</i>	6	10
Pain and bleeding, <i>n</i>	1	1
Pain and stenosis, <i>n</i>	1	–
Stenosis, <i>n</i>	1	–
Pain caused by fissure, <i>n</i>	1	2
Constipation and urinary retention, <i>n</i>	–	2
Bleeding, <i>n</i>	6	1
Constipation, <i>n</i>	–	3
Pain and constipation, <i>n</i>	–	1
Constipation and bleeding, <i>n</i>	–	2
Pain, constipation and bleeding, <i>n</i>	–	1
Anaesthesia, <i>n</i>	–	2
Haemorrhoids symptoms, <i>n</i>	1	–
Fissure, <i>n</i>	1	–

^a One participant in each group experienced two SAEs of pain.

Subgroup analysis

Two subgroup analyses were planned on the primary outcome (EQ-5D-3L AUC over 24 months): sex and grade of haemorrhoid.

A stricter level of statistical significance (two-sided 1% significance level) was applied given the exploratory nature of the analyses.

There was no evidence that any of the subgroups were statistically different at the 1% level; the results are shown in *Tables 30* and *31*.

TABLE 30 Subgroup analysis at 24 months: participants need to have at least one short-term and one long-term follow-up score

	Trial arm, <i>n</i> , mean (SD)			
Outcome	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)	MD (99% CI)	<i>p</i> -value
Sex				
Female	147, 1.531 (0.502)	126, 1.626 (0.414)	–	–
Male	148, 1.582 (0.464)	149, 1.612 (0.446)	0.055 (–0.087 to 0.197)	0.295
Grade of haemorrhoid				
II	56, 1.545 (0.492)	60, 1.532 (0.467)	–	–
III	196, 1.564 (0.483)	171, 1.657 (0.408)	–0.072 (–0.300 to 0.155)	0.388
IV	43, 1.536 (0.482)	44, 1.585 (0.458)	0.050 (–0.302 to 0.403)	0.696

TABLE 31 Subgroup analysis: participants with at least one long-term follow-up score over 24 months

	Trial arm, <i>n</i> , mean (SD)			
Outcome	SH (<i>N</i> = 388)	TH (<i>N</i> = 386)	MD (99% CI)	<i>p</i> -value
Sex				
Female	158, 1.510 (0.505)	139, 1.613 (0.427)	–	–
Male	157, 1.572 (0.472)	155, 1.605 (0.444)	0.056 (–0.083 to 0.196)	0.272
Grade of haemorrhoid				
II	61, 1.518 (0.507)	67, 1.544 (0.446)	–	–
III	206, 1.546 (0.491)	183, 1.638 (0.425)	–0.036 (–0.265 to 0.192)	0.663
IV	48, 1.548 (0.465)	44, 1.585 (0.458)	0.090 (–0.249 to 0.430)	0.468

Chapter 6 Health economics

The perspective of the analyses is primarily that of the UK NHS. A supplementary analysis incorporates wider perspective costs, including participant travel costs, opportunity costs of time spent attending appointments for participants and companions, self-purchased health care and time off work as a result of haemorrhoidal surgery. The last analysis provides a wider scope on the economic consequences of haemorrhoidal surgery.

Over the 24-month study period, some participants were missing data from the key parameters for the analysis, such as the EQ-SD-3L score at the different time points, as well as resource use data. The results (*Table 32*) show that the number of missing data was broadly similar between arms and also increased over time.

Resource use

The details of the resources used for the surgical procedure, such as type of surgery, type of stapler used, operating surgeon grade, anaesthetist grade, type of anaesthesia, duration of operation and length of hospital stay, are reported (see *Table 9*). On average, the use of resources was similar across both arms. Details of the number of participants receiving further surgical interventions, such as removal of skin tags, TH, SH and RBL, are reported (see *Table 21*). The number of further interventions, was low over the 24-month period. For example, at the 6-week time point, eight participants received TH: six in the SH arm and two in the TH arm. Three participants (in the SH arm) and one (in the TH arm) received SH, while four (in the SH arm) and six (in the TH arm) had RBL. Five participants (in the SH arm) and four (in the TH arm) had further treatments for skin tags. The number of participants receiving non-surgical treatments, such as Botox and medical treatments, are reported (see *Table 22*). Further non-surgical interventions resource use was similar for both arms at 6 weeks post treatment. Further non-surgical interventions resource use was higher in the SH arm at 12 months (54 vs. 31 participants) and 24 months (39 vs. 19 participants). *Table 33* below details participant-reported visits to outpatient department and GP. On average there were more visits in the SH arm.

TABLE 32 Missing data for key variables used in the cost-effectiveness analysis

Variable	Trial arm, <i>n</i> (%)		% difference	All participants, <i>n</i> (%)
	SH (<i>N</i> = 389)	TH (<i>N</i> = 386)		
EQ-5D-3L				
Baseline	1 (0.26)	0 (0)	0.26	1 (0.13)
1 week	91 (23.39)	95 (24.61)	−1.22	186 (23.94)
3 weeks	104 (26.74)	110 (28.5)	−1.76	214 (27.54)
6 weeks	84 (21.59)	83 (21.5)	0.09	167 (21.49)
12 months	98 (25.19)	112 (29.02)	−3.83	210 (27.03)
24 months	106 (27.25)	114 (29.53)	−2.28	220 (28.31)
QALYs	183 (47.04)	192 (49.74)	−2.7	375 (48.26)
Costs				
Intervention	48 (12.34)	26 (6.74)	5.6	74 (9.52)
12 months	174 (44.73)	171 (44.30)	0.43	345 (44.40)
24 months	145 (37.28)	153 (39.64)	−2.36	298 (38.35)
Total cost	213 (54.76)	208 (53.89)	0.87	421 (54.18)

TABLE 33 Summary of participant-reported visits to outpatient department and GP

Resource	Trial arm, <i>n</i> , mean (SD)	
	SH (<i>N</i> = 389)	TH (<i>N</i> = 386)
12 months		
Visit to outpatient department	80, 1.74 (1.00)	55, 1.51 (0.81)
Visit to GP (doctor)	63, 2.02 (1.24)	47, 1.85 (1.43)
Visit to GP (nurse)	12, 1.58 (1.24)	8, 1.38 (0.74)
Visit to other professionals	11, 2.45 (1.75)	7, 2.86 (3.24)
24 months		
Visit to outpatient department	27, 1.89 (1.15)	15, 1.47 (0.92)
Visit to GP (doctor)	46, 2.00 (1.74)	20, 1.70 (0.86)
Visit to GP (nurse)	6, 2.17 (1.47)	2, 1.50 (0.71)
Visit to other professionals	5, 1.60 (0.89)	3, 1.00 (0.00)

The average surgery time used in the economic analysis was estimated using all available data. A few participants were missing either time of entry into the operating room and/or the time of leaving the operating room, so their time was estimated using available data. No data were collected on the time spent in the recovery room as it was assumed that this would have been similar in both treatment arms; it was therefore not included in the estimation of resource use.

Tables 34 and *35* detail the conversions of all the resource use into costs to the NHS and cost differences between the two arms. The estimates are reported in terms of NHS costs (see *Table 34*) incurred after the participant received the treatments. The mean total cost per patient in the SH arm was £921.80 (SD £586.90) and the mean cost of treatment in the TH arm was £620.65 (SD £582.98). There was a statistically significant difference in the (adjusted) total mean costs (£323, 95% CI £237 to £409) of the interventions.

The cost results reflect resource use results. A low level of resource use means that total cost data were skewed to the right, as most of the participants had low or no costs at all, but a few had high costs. *Figures 6* and *7* illustrate the distribution of SH and TH costs, respectively.

Although cost of resource use measured during the intervention was similar in both arms, the mean cost of interventions was £272.62 higher in the SH arm (95% CI £239.74 to £305.66) because of the additional costs of the staplers (see *Table 35*). The costs reported at the 6-week visit were £25.34 lower in the SH arm (95% CI –£67.80 to £17.12), but not statistically significant. The other patient-reported costs between 6 months and 12 months were higher for SH (MD £32.96, 95% CI –£1.82 to £67.74) but not statistically significant, and the total 12-month costs were significantly higher in the SH arm (MD £308.50, 95% CI £237.08 to £379.93) than in the TH arm. The 12- to 24-month costs were significantly higher in the SH arm (MD £47.57, 95% CI £13.32 to £81.82). Total mean costs over the 24-month follow-up period were significantly higher in the SH arm (MD £323.38, 95% CI £237.11 to £409.64) than in the TH arm. The incremental differences are based on linear regression models, namely ordinary least squares with adjustments for baseline covariates, including baseline EQ-5D-3L score.

TABLE 34 Mean NHS costs for study interventions (unadjusted)

Resource	Trial arm, <i>n</i> , mean cost (£) (SD)	
	SH (<i>N</i> = 389)	TH (<i>N</i> = 386)
Intervention		
Staff time at operation	349, 207.94 (81.76)	360, 212.53 (87.69)
Anaesthetic used	356, 14.06 (2.51)	361, 14.25 (2.17)
Stapler	346, 306.70 (153.83)	362, 32.20 (111.10)
Admissions during intervention	354, 51.45 (134.22)	362, 48.57 (145.33)
Total intervention cost	341, 581.06 (230.22)	360, 308.00 (215.47)
6-week follow-up		
6-week clinic visit	348, 102.79 (45.08)	357, 98.14 (48.97)
Additional hospital visit	348, 10.32 (42.11)	357, 12.55 (46.07)
Proctoscopy	305, 3.03 (4.92)	305, 3.03 (4.92)
Further intervention	348, 12.67 (99.61)	356, 18.91 (134.37)
Admissions	348, 25.26 (253.27)	355, 46.88 (279.80)
Prescribed medicines	348, 3.45 (14.77)	356, 3.31 (15.24)
Total 6-week cost	305, 150.89 (313.94)	304, 175.49 (389.75)
12 months		
Outpatient appointments	274, 62.02 (117.10)	258, 39.33 (88.37)
GP (doctor)	276, 20.25 (45.38)	259, 14.78 (41.16)
GP (nurse)	278, 0.83 (4.93)	259, 0.52 (3.25)
Other health professionals	277, 6.01 (44.02)	250, 1.51 (13.70)
Medicines prescribed	258, 2.16 (7.71)	236, 1.63 (6.58)
Admissions	264, 61.77 (306.51)	249, 32.73 (204.92)
Total after 6-week visit	243, 138.28 (334.77)	227, 80.56 (251.56)
Total cost to 12 months	197, 869.23 (578.73)	188, 547.42 (446.67)
24 months ^a		
Further intervention	257, 36.18 (191.37)	241, 20.75 (144.20)
Admissions	256, 30.67 (238.69)	241, 16.22 (111.87)
Outpatient appointments	258, 25.64 (81.99)	244, 10.65 (49.12)
GP (doctor)	258, 15.98 (45.04)	244, 5.92 (22.37)
GP (nurse)	258, 0.59 (4.53)	245, 0.19 (1.83)
Other health professionals	258, 3.12 (26.51)	245, 1.03 (10.14)
Medicines prescribed	245, 0.67 (2.94)	236, 0.29 (1.27)
Total 12–24 months ^a	244, 102.41 (365.79)	233, 56.49 (219.22)
Total over the 2 years	158, 921.80 (586.90)	156, 620.65 (582.98)

^a 24-month data were discounted at 3.5%.

TABLE 35 Mean cost differences for the NHS for complete cases (adjusted)

Resource	MD ^a (95% CI)	Standard error	p-value
Intervention			
Time of staff at operation	-4.95 (-18.40 to 8.50)	6.57	0.46
Anaesthetic used	-0.19 (-0.53 to 0.15)	0.17	0.27
Stapler	274.52 (207.35 to 341.70)	32.79	0.00
Admissions	2.56 (-21.62 to 26.75)	11.81	0.83
Total intervention	272.62 (239.74 to 305.66)	36.79	0.00
6-week follow-up			
Proctoscopy	0.05 (-0.51 to 0.61)	0.27	0.85
6-week follow-up visit	4.35 (-0.18 to 8.90)	2.21	0.06
Additional hospital visit	-2.31 (-9.69 to 5.07)	3.60	0.53
Further intervention	-5.87 (-21.28 to 9.55)	7.53	0.44
Inpatient stay	-21.91 (-53.30 to 9.48)	15.32	0.16
Prescribed medicines	0.12 (-1.49 to 1.73)	0.78	0.88
Intervention: 6-week costs	-25.34 (-67.80 to 17.12)	20.73	0.23
12 months			
Further interventions	25.69 (-23.30 to 74.67)	23.91	0.29
Outpatient appointment	23.73 (7.39 to 40.06)	7.98	0.01
GP (doctor)	5.86 (-1.64 to 13.36)	3.66	0.12
GP (nurse)	0.39 (-0.31 to 1.08)	0.34	0.26
Other health professionals	4.39 (1.47 to 7.32)	1.43	0.01
Medicines prescribed	0.54 (-0.70 to 1.78)	0.60	0.38
Inpatient stay	1.43 (-4.52 to 7.38)	2.91	0.63
6-week: 12-month costs	32.96 (-1.82 to 67.74)	16.95	0.06
Total 12-month costs	308.50 (237.08 to 379.93)	34.75	0.00
24 months			
Further interventions	16.86 (-11.94 to 45.67)	14.06	0.24
Outpatient appointment	15.45 (3.52 to 27.38)	5.82	0.01
GP (doctor)	10.20 (5.73 to 14.67)	2.18	0.00
GP (nurses)	0.40 (-0.14 to 0.93)	0.26	0.14
Other health professionals	2.18 (-0.73 to 5.09)	1.42	0.14
Medicines prescribed	0.40 (0.03 to 0.76)	0.18	0.03
Inpatient stay	15.86 (-10.93 to 42.66)	13.08	0.24
12-24 ^b months costs	47.57 (13.32 to 81.82)	16.72	0.01
Total cost over the 24 months	323.38 (237.11 to 409.64)	41.97	0.00

a Cost difference adjusted for minimisation covariates and baseline EQ-5D-3L score.

b 24-month costs discounted at 3.5%. Positive cost difference values indicate that SH costs more than TH and vice versa.

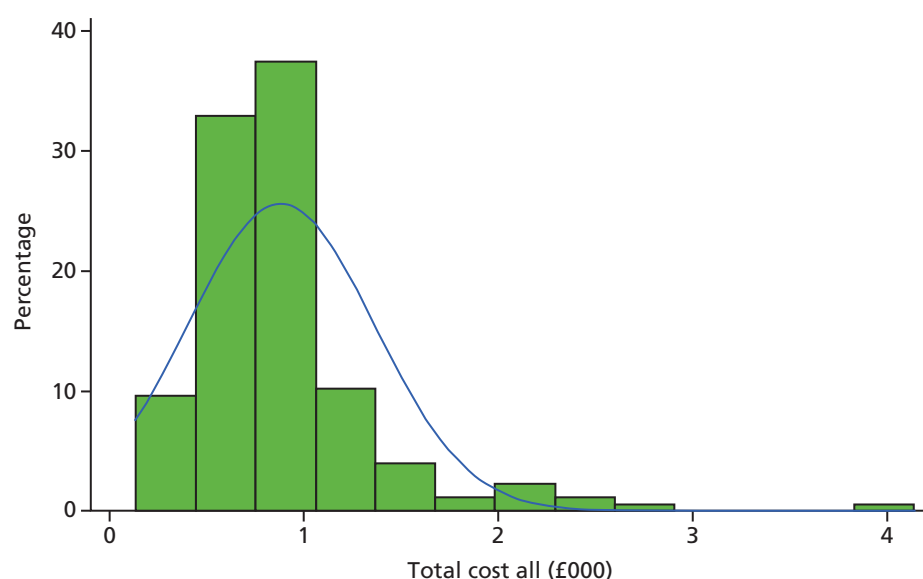


FIGURE 6 Distribution of cost data in the SH arm.

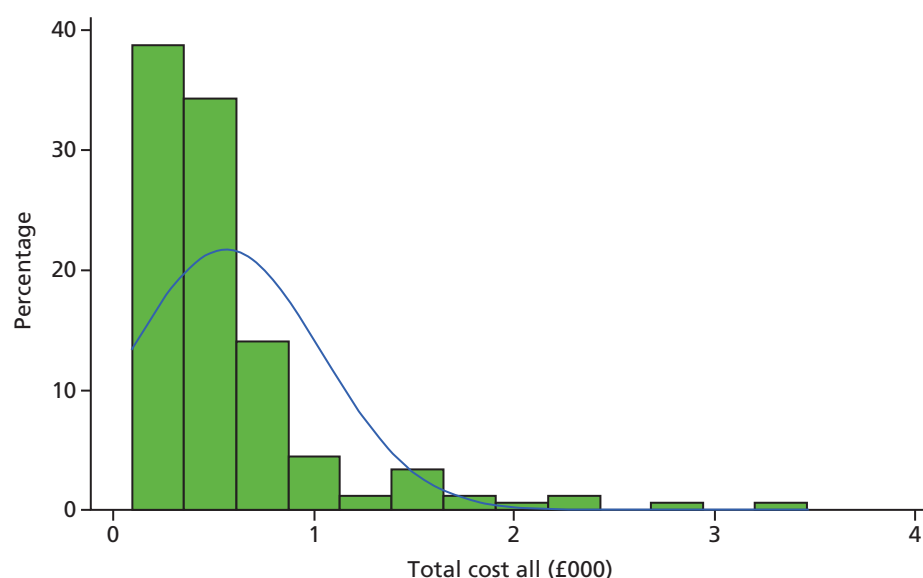


FIGURE 7 Distribution of data in the TH arm.

Quality-adjusted life-years

The EQ-5D-3L scores for the study arms at baseline, at 1 week, 3 weeks, 6 weeks, and at 12 and 24 months are shown in *Table 36*. The EQ-5D-3L scores were higher in the SH arm at 1 week and 3 weeks. However, the scores were lower at 6 weeks, 12 months and 24 months. From these data it was estimated that the mean QALYs over the 2 years were 1.676 (SD 0.384) in the SH arm and 1.738 (SD 0.334) in the TH arm.

The MD between the arms in EQ-5D-3L score at 1 week, 3 weeks, 6 weeks, and at 12 and 24 months are reported below (*Table 37*). The MD in EQ-5D-3L scores after adjusting for minimisation factors and baseline EQ-5D-3L scores was statistically significantly higher for SH at 1 week (MD 0.135, 95% CI 0.082 to 0.188) and 3 weeks (MD 0.05, 95% CI 0.008 to 0.091), but was significantly lower at 12 months and 24 months. The QALY difference was -0.071 (95% CI -0.127 to -0.016) and was statistically significantly lower for the SH arm than the TH arm.

TABLE 36 Quality-of-life scores for each study intervention

Time point	Trial arm, <i>n</i> , mean (SD)	
	SH (<i>N</i> = 389)	TH (<i>N</i> = 386)
Baseline	388, 0.762 (0.247)	386, 0.764 (0.264)
1 week	298, 0.592 (0.315)	291, 0.458 (0.337)
3 weeks	285, 0.802 (0.244)	276, 0.750 (0.244)
6 weeks	305, 0.846 (0.220)	303, 0.851 (0.235)
12 months	291, 0.822 (0.252)	274, 0.880 (0.209)
24 months ^a	283, 0.802 (0.242)	272, 0.841 (0.192)
QALYs ^b	206, 1.676 (0.384)	194, 1.738 (0.334)

a The 24-month EQ-5D-3L score was discounted at 3.5% per annum.
b QALYs gained are based on an AUC, and the EQ-SD-3L scores are point estimates at specific times.

TABLE 37 Mean difference for utility scores from the difference time points

Time point	MD (95% CI)	Standard error	<i>t</i>	<i>p</i> > <i>t</i>
Week 1	0.135 (0.082 to 0.188)	0.026	5.230	0.000
Week 3	0.050 (0.008 to 0.091)	0.020	2.460	0.021
Week 6	−0.004 (−0.037 to 0.029)	0.016	−0.230	0.817
12 months	−0.064 (−0.095 to −0.033)	0.015	−4.210	0.000
24 months ^a	−0.046 (−0.079 to −0.013)	0.016	−2.860	0.008
QALYs ^b	−0.071 (−0.127 to −0.016)	0.027	−2.650	0.013

a The 24-month EQ-5D-3L score was discounted at 3.5% per annum.
b QALYs gained are based on an area under a curve, and the EQ-SD-3L scores are point estimates at specific times.
Positive values suggest that SH is more clinically effective than TH and vice versa.

Cost-utility results

The base-case analysis was based on multiple imputed data. The estimated costs and QALYs are reported below (Table 38). Total cost was £337 (95% CI £251 to £423). Total QALYs were lower in the SH group (MD −0.074, 95% CI −0.127 to −0.011). Both these differences are statistically significant.

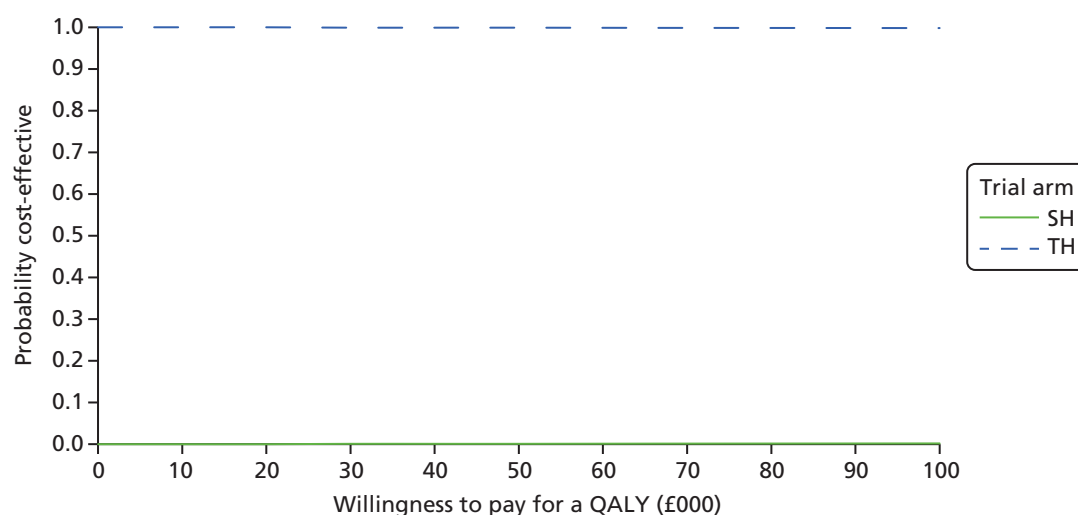
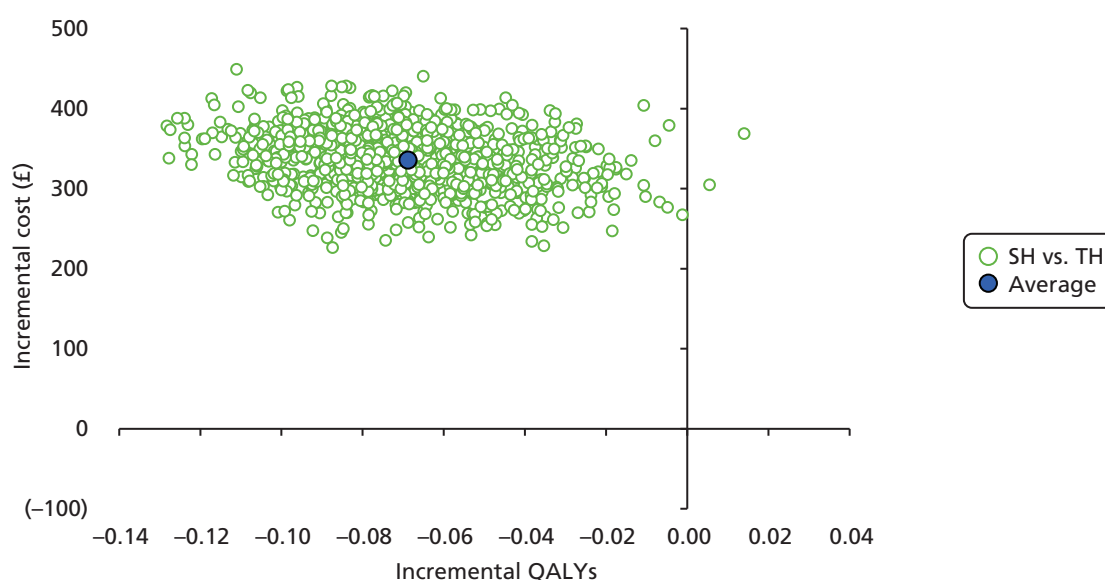
The CEAC generated from the base-case cost-effectiveness analysis (Figure 8) shows that there is no probability of SH being cost-effective at the thresholds of £20,000 and £30,000.

The scatterplot (Figure 9) shows the point estimate and the distribution of the joint differences in costs and effects. The ICER point estimate and almost all of the bootstrapped estimates fall in the north-west quadrant of the cost-effectiveness plane, suggesting that SH is significantly more costly and less clinically effective than TH.

TABLE 38 Estimation of cost–utility analysis

Arm	Cost (£), mean (SD)	Cost (£) difference (£) (standard error), 95% CI	QALY, mean (SD)	Difference (standard error), 95% CI	ICER
SH (n = 389)	941 (415)	–	1.62 (0.43)	–	Dominated ^a
TH (n = 386)	602 (507)	337 (41), 251 to 423	1.69 (0.38)	–0.070 (0.027), 0.127 to –0.011	–

a Dominated = it costs more and is less clinically effective.

**FIGURE 8** Cost-effectiveness acceptability curve showing the probability that SH is cost-effective, given the different values of WTP thresholds.**FIGURE 9** Cost-effectiveness scatterplot illustrating the distribution of differences in costs and QALYs.

Cost-effectiveness results: number of recurrences averted

The results of the cost-effectiveness analysis based on the number of recurrences averted were similar to those of the base-case analysis (*Table 39*). On average, there were more recurrences in the SH arm and SH was more costly than TH. SH was dominated by TH.

Subgroup analysis

The results allowing for a treatment interaction with sex provide similar results to those of the base-case analysis. On average, SH cost £334.78 more than TH and had –0.069 QALYs fewer than TH. There was a 2.4% probability of being considered cost-effective at a £30,000 threshold (*Figure 10*).

The ICER plot estimate falls in the north-west quadrant of the cost-effectiveness plane, suggesting that SH is more costly and less clinically effective than TH (*Figure 11*).

The results of the subgroup analysis incorporating a treatment interaction with haemorrhoidal grade were broadly similar to those of the base-case analysis. Allowing for grade-specific effects, on average, SH had higher costs and lower QALYs than TH. However, the chance that SH might be considered to be cost-effective at the £30,000 threshold increased to 6% (*Figure 12*).

TABLE 39 Estimation of cost-effectiveness based on number of recurrences

Arm	Cost (£), mean (SD)	Cost (£) difference (standard error), 95% CI	Recurrences, mean (SD)	Difference (standard error), 95% CI	ICER
SH (n = 389)	941 (415)	–	0.327 (0.008)	–	Dominated ^a
TH (n = 386)	602 (507)	337 (41), 251 to 423	0.142 (0.006)	–0.18 (0.030), –0.245 to –0.120	–

a Dominated = it costs more and has more recurrences.

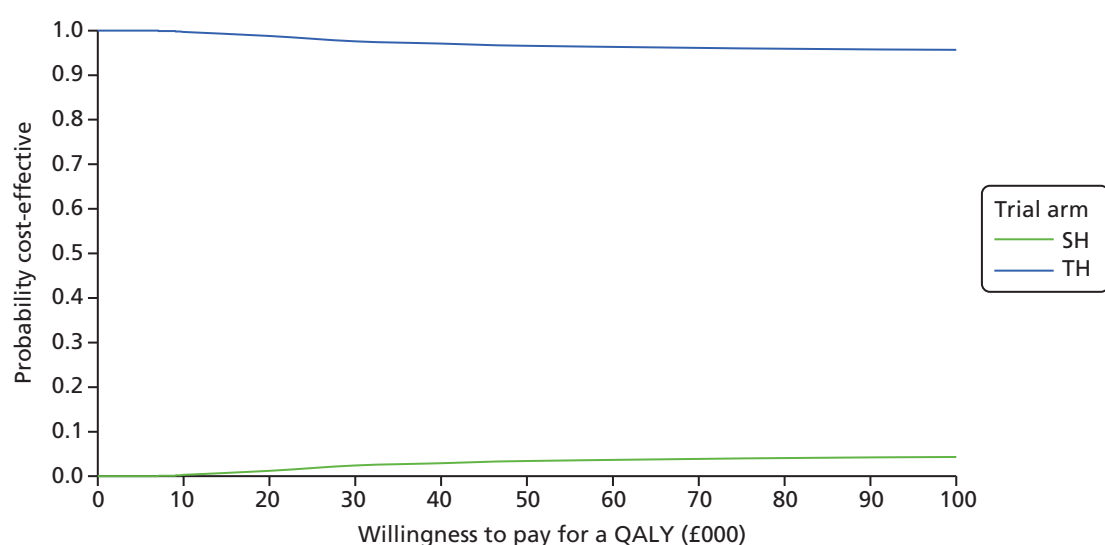


FIGURE 10 Cost-effectiveness acceptability curve showing the probability that SH is cost-effective, given the different values of WTP thresholds for subgroup analysis investigating the influence of sex.

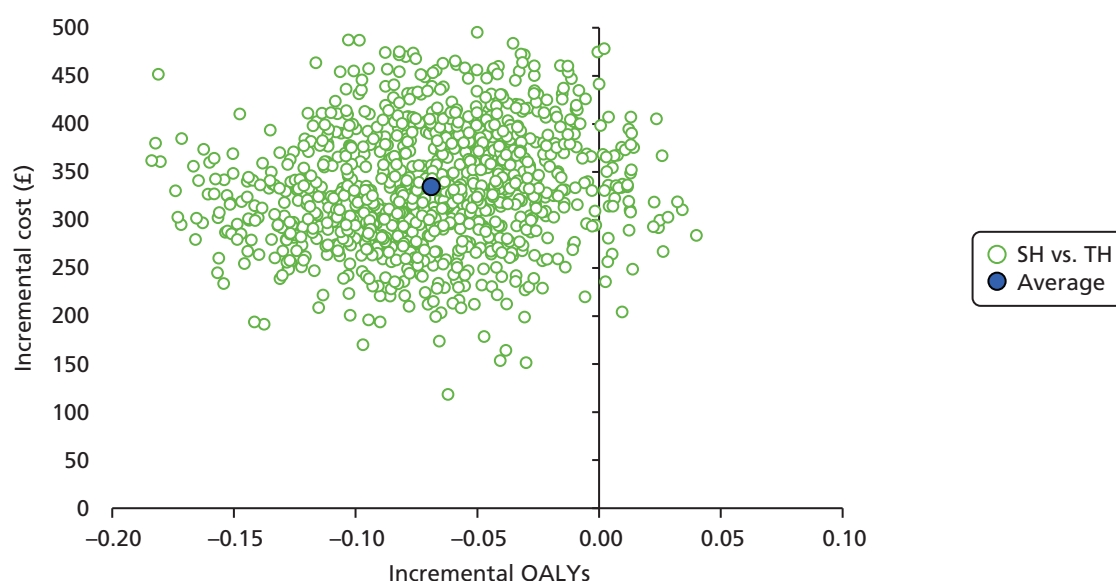


FIGURE 11 Cost-effectiveness scatterplot illustrating the distribution differences of costs and QALYs for the analysis interacting treatment with sex.

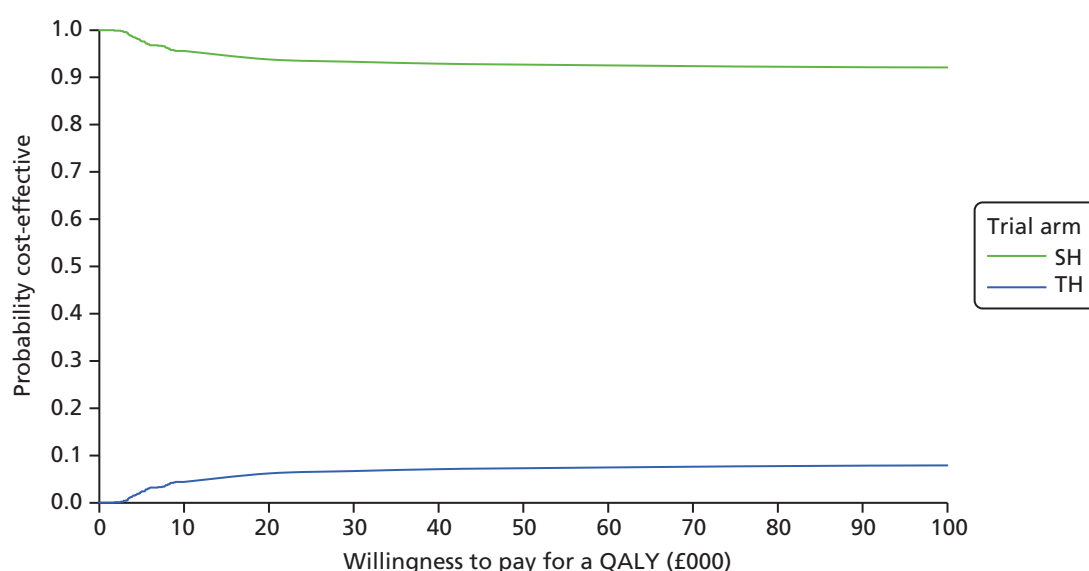


FIGURE 12 Cost-effectiveness acceptability curve showing the probability that SH is cost-effective, given the different values of WTP thresholds for subgroup analysis incorporating a treatment interaction with haemorrhoidal grade.

The ICER plot estimate falls in the north-west quadrant of the cost-effectiveness plane, suggesting that SH is more costly and less clinically effective than TH (Figure 13).

Sensitivity analysis

Complete-case analysis

The results of the analysis considering the complete cases (based on participants with both cost and QALY data) are presented in Table 40. On average, SH cost £287.87 (95% CI £190.17 to £385.56) more than TH and had -0.060 (95% CI -0.113 to -0.007) fewer QALYs than TH.

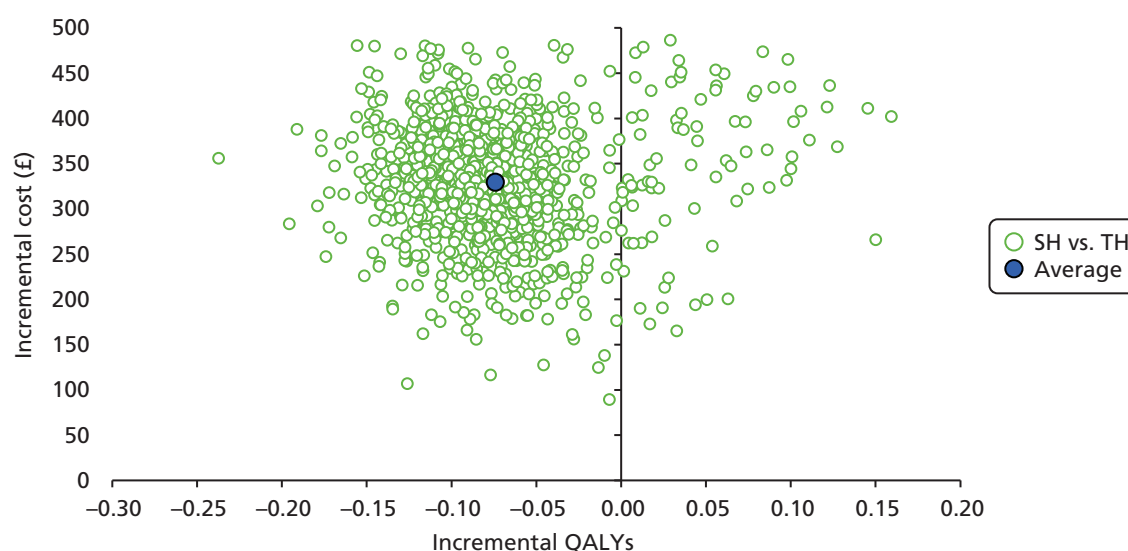


FIGURE 13 Cost-effectiveness scatterplot illustrating the distribution of differences in costs and QALY for the analysis incorporating a treatment interaction with haemorrhoidal grade.

TABLE 40 Estimation of cost-effectiveness (complete-case analysis)

Trial arm	Costs (£), <i>n</i> , mean (SD)	Cost (£) difference (standard error), 95% CI	QALY, <i>n</i> , mean (SD)	Difference (standard error), 95% CI	ICER
SH (<i>N</i> = 389)	148, 863.91 (415)	–	148, 1.72 (0.33)	–	Dominated ^a
TH (<i>N</i> = 386)	149, 573.27 (507)	287.87 (47.33), 190.17 to 385.56	149, 1.77 (0.30)	–0.060 (0.026), –0.113 to –0.007	–

^a Dominated = it costs more and is less clinically effective.

The results of the complete-case analysis were broadly similar to those of the base-case analysis. On average, SH had higher costs and fewer QALYs than TH. The probability that SH might be considered to be cost-effective at the £30,000 threshold was 1.7% (Figure 14).

The ICER plot estimate falls in the north-west quadrant of the cost-effectiveness plane, showing SH to be more costly and less clinically effective than TH (Figure 15).

Sensitivity analysis using Short Form questionnaire-36 items data

The utility and QALY scores derived from the SF-36D followed a similar pattern to those of the EQ-5D-3L (Table 41). On average, the 6-week utility score in the SH arm was –0.015 lower than that in the TH arm, but this did not meet statistical significance. However, the utility score was also lower at 12 months (–0.040) and 24 months (–0.034), and these differences were statistically significant ($p < 0.05$) (Table 42). The number of QALYs was –0.063 (95% CI –0.107 to –0.018) lower in the SH arm than in the TH arm.

The CEAC (Figure 16) indicates that there is only a 0.1% chance of SH being considered cost-effective at WTP thresholds of £20,000 or £30,000 (based on QALYs derived from the SF-6D). The ICER plot estimate falls in the north-west quadrant of the cost-effectiveness plane, suggesting that SH is more costly and less clinically effective than TH (Figure 17).

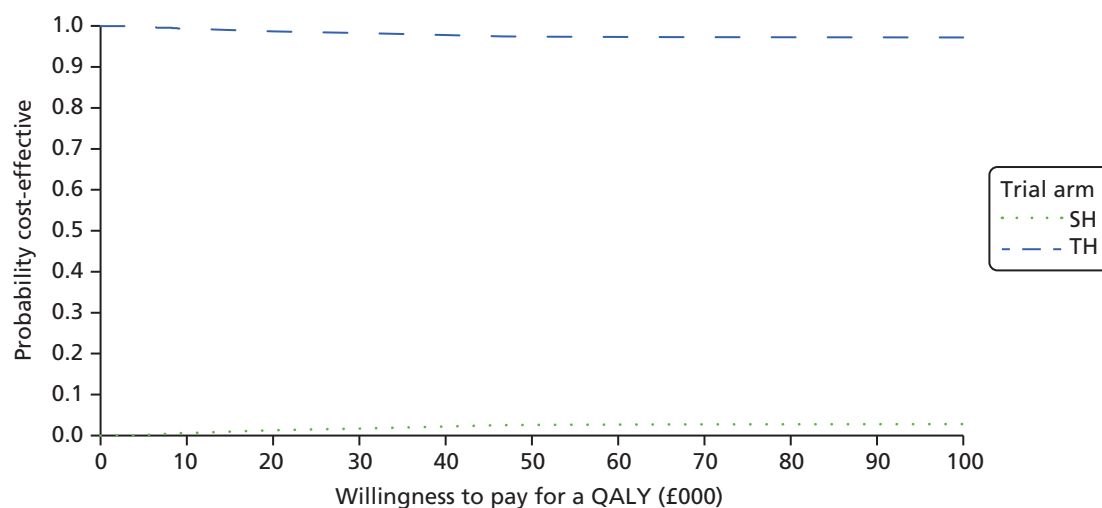


FIGURE 14 Cost-effectiveness acceptability curve showing the probability that SH is cost-effective, given the different values of WTP thresholds (complete-case analysis).

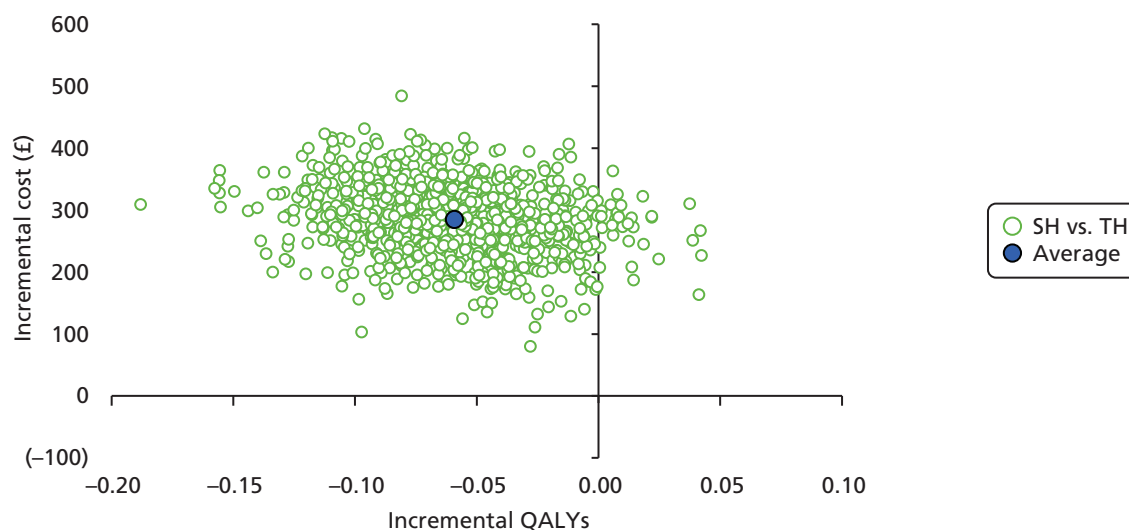


FIGURE 15 Cost-effectiveness scatterplot illustrating the distribution of differences in costs and QALYs for sensitivity analysis (complete-case analysis).

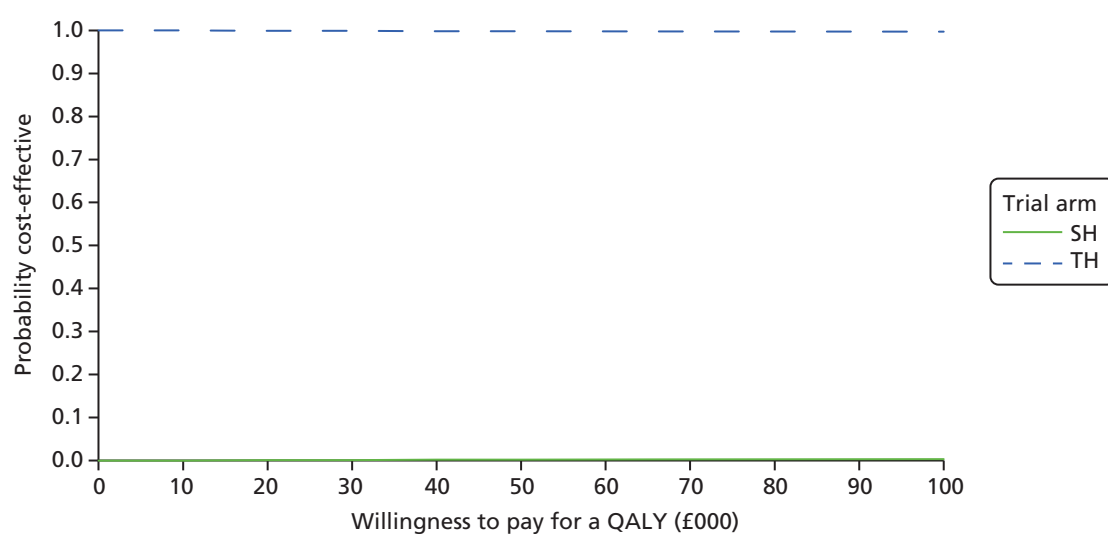
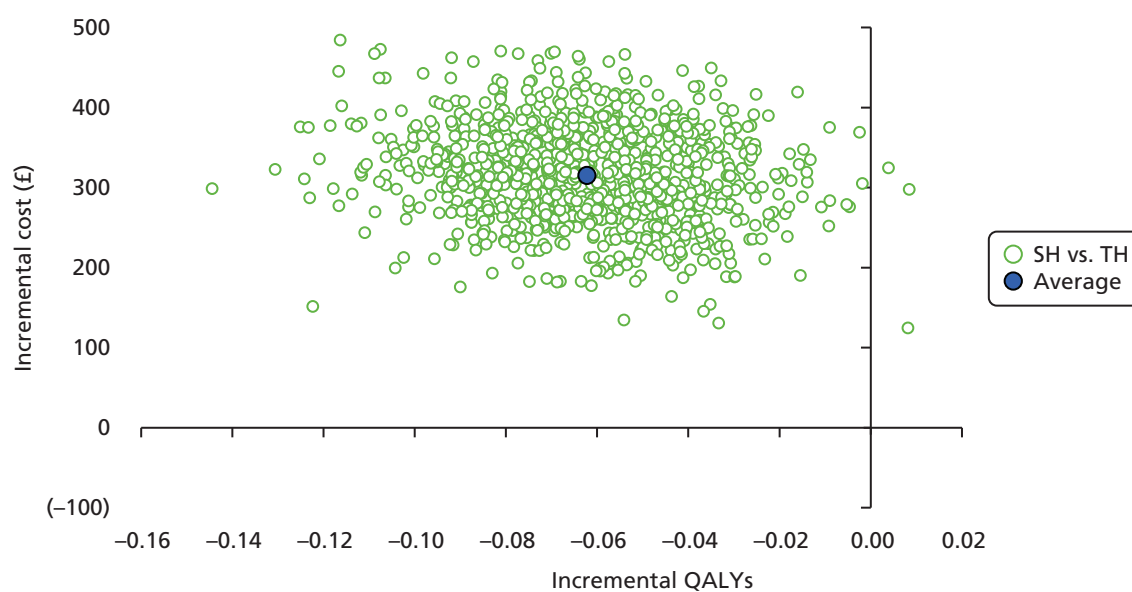
TABLE 41 Sensitivity analysis using SF-36 data converted to SF-6D data

Time point	Trial arm, <i>n</i> , mean score (SD)	
	SH (<i>N</i> = 389)	TH (<i>N</i> = 386)
Baseline	376, 0.736 (0.144)	370, 0.745 (0.143)
6 weeks	255, 0.741 (0.142)	268, 0.747 (0.148)
12 months	254, 0.758 (0.154)	241, 0.796 (0.147)
24 months	239, 0.776 (0.144)	222, 0.800 (0.131)
QALYs	161, 1.540 (0.263)	156, 1.600 (0.238)

TABLE 42 Sensitivity analysis using SF-6D data (MD at different time points)

Time point	MD (95% CI)	Standard error	<i>t</i>	<i>p</i> -value
6 weeks	−0.015 (−0.37 to 0.007)	0.010	−1.32	0.168
12 months	−0.040 (−0.070 to −0.010)	0.015	−2.73	0.012
24 months ^a	−0.034 (−0.062 to −0.006)	0.013	−2.52	0.019
QALYs	−0.063 (−0.107 to −0.018)	0.021	−2.92	0.008

^a Discounted at 3.5% QALYs.

**FIGURE 16** Cost-effectiveness acceptability curve showing the probability that SH is cost-effective, given the different values of WTP thresholds: sensitivity analysis using SF-6D data.**FIGURE 17** Cost-effectiveness scatterplot illustrating distribution of cost and QALY differences for sensitivity analysis (SF-6D data).

Sensitivity relating to cost of staplers

Further analysis was undertaken varying the cost of the staplers and using the least expensive of those used in the study (Table 43). The QALY difference remains the same as before (−0.070, 95% CI −0.127 to −0.011) (see Table 38). The results were similar to those of the base-case analysis. For costs of ≥ £125, SH costs significantly more and has fewer QALYs than TH. SH remains marginally more costly than TH, unless the cost of the stapler falls to zero.

The results of the analysis in which it was assumed that there was no additional cost of staplers suggest that SH has a 0.1% chance of being considered cost-effective at the £20,000 and £30,000 thresholds (Figure 18).

The ICER plot estimate falls in the north-west quadrant of the cost-effectiveness plane, suggesting that SH is more costly and less clinically effective than TH (Figure 19). The cost difference estimate is lower (£216) than that of the base case (£323), so the ellipse is lower than that of the base case.

TABLE 43 Cost differences at different costs of staplers

Cost of stapler (£)	Cost (£) difference (95% CI)	Standard error	t	p-value	ICER
269	216.45 (123.62 to 309.28)	45.07	4.80	0.000	SH dominated
150	118.55 (30.83 to 206.28)	42.60	2.78	0.010	SH dominated
125	98.10 (11.14 to 185.05)	42.22	2.32	0.029	SH dominated
100	77.64 (−8.67 to 163.93)	41.90	1.85	0.076	SH dominated
75	57.18 (−28.57 to 142.92)	41.64	1.37	0.182	SH dominated
50	36.72 (−48.61 to 122.03)	41.42	0.89	0.384	SH dominated
45	32.62 (−52.62 to 117.87)	41.40	0.79	0.438	SH dominated
0	−4.20 (−89.0 to 80.59)	41.17	−0.10	0.919	60

The cost difference indicates that SH costs less than TH (not statistically significant) and is less effective; therefore, it is not likely that it would be considered cost-effective.

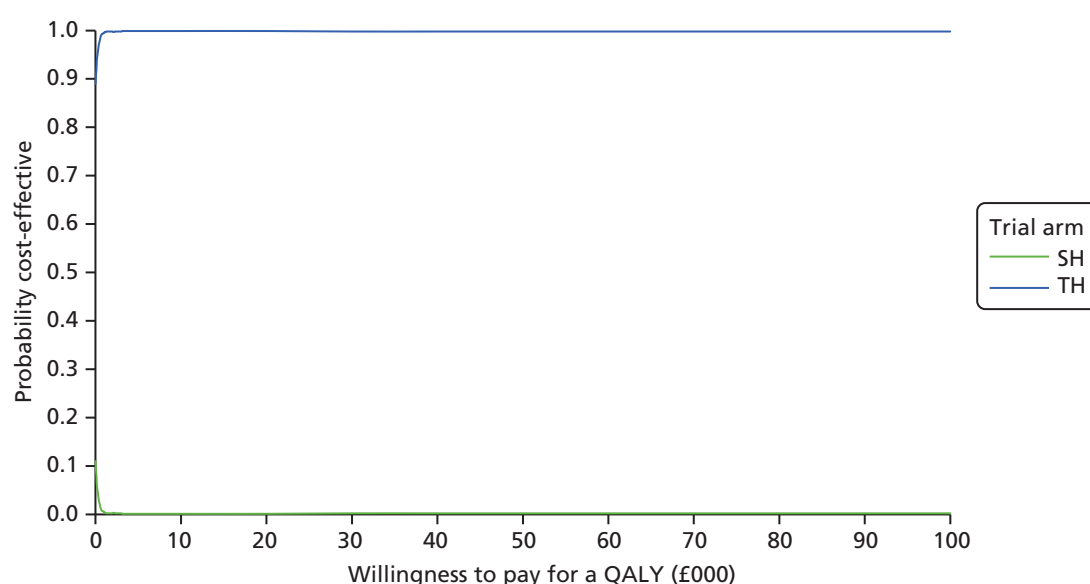


FIGURE 18 Cost-effectiveness acceptability curve showing the probability that SH is cost-effective, given the different values of WTP thresholds: assuming no cost of stapler.

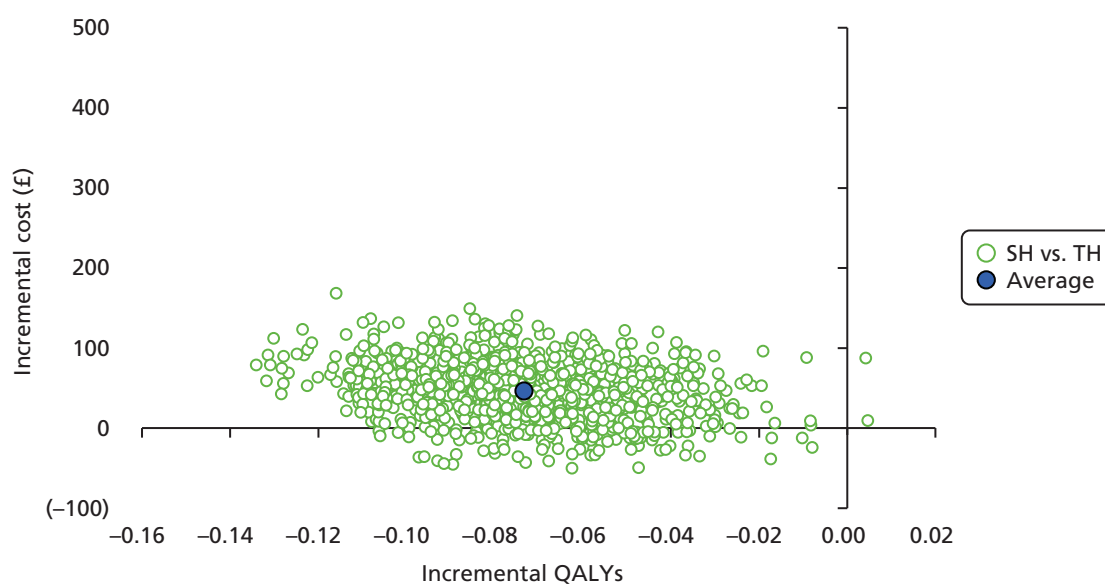


FIGURE 19 Cost-effectiveness scatterplot illustrating the distribution of cost and QALY differences: sensitivity analysis assuming no cost of stapler.

Participant costs

The distribution patterns of the participant costs are similar to those of the main analysis (*Figures 20 and 21*). There are many participants with low costs and very few with high costs. The average participant costs were £31.48 (95% CI £5.00 to £57.00) higher for SH (£69.83, SD 229.33) than for TH (£38.35, SD 72.80). This further increases the total cost difference between the arms.

The cost-utility analysis based on the imputed data is reported in *Table 44*. On average, the cost indicates that the SH arm has £326.11 higher costs and -0.070 fewer QALYs than the TH arm. Like the base-case analysis, there was no chance that SH would be cost-effective at the £20,000 threshold and a 0.1% chance that it would be cost-effective at the £30,000 threshold (*Figure 22*).

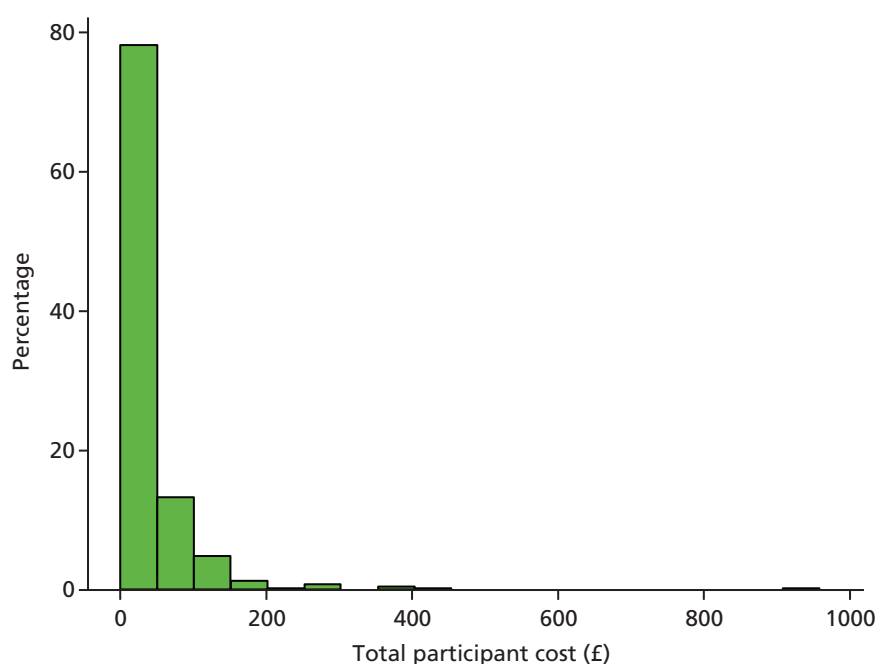


FIGURE 20 Distribution of total participant costs in the SH arm.

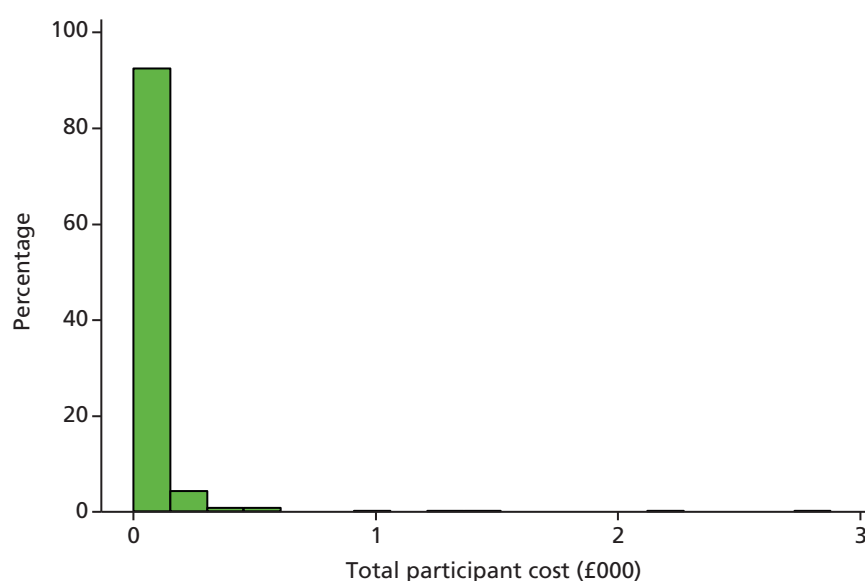


FIGURE 21 Distribution of total participant costs in the TH arm.

TABLE 44 Cost–utility analysis results for societal costs^a

Variable	MD (95% CI)	Standard error	p-value	ICER
Costs (£)	326.11 (215.02 to 437.20)	53.94	0	–
QALYs	–0.070 (–0.127 to –0.011)	0.027	0.11	SH dominated

^a Societal means both NHS and participant costs.

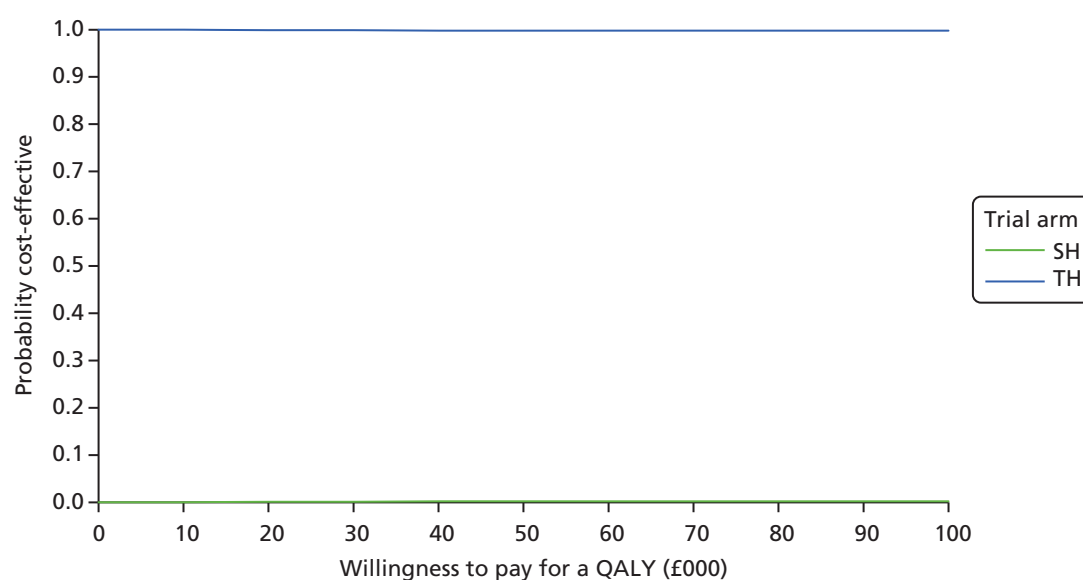


FIGURE 22 Cost-effectiveness acceptability curve showing the probability that SH is cost-effective, given the different values of WTP thresholds: sensitivity analysis including societal cost.

The ICER plot estimate falls in the north-west quadrant of the cost-effectiveness plane, suggesting that SH is more costly and less clinically effective than TH (*Figure 23*).

Discussion

Summary of the main findings

The results of the base-case analysis suggest that, on average, SH costs £337 more than TH and has -0.0704 fewer QALYs than TH. The cost-utility analysis suggests that there is no chance of SH being considered cost-effective at £20,000, and a very low chance of being considered cost-effective (0.01%) at the £30,000 WTP threshold. Similar results are seen in all the analyses that were conducted. The sensitivity analyses using the complete cases and SF-6D were similar to the base-case results: SH always costs more than TH and generates fewer QALYs than TH. Results of the analysis incorporating subgroup interaction terms relating to sex were similar to those of the base-case analysis, but those of the analysis incorporating an interaction for the grade of haemorrhoid had a higher chance (6%) of SH being considered to be cost-effective at a WTP threshold of £30,000.

The major driver for the increased cost of SH was the cost of staplers, but the sensitivity analysis shows that the cost-effectiveness conclusions are not particularly sensitive to this parameter, because of the superior QALY estimates for TH. This was a pragmatic study and study sites were allowed to use the stapler of their choice. Sensitivity analyses varying the cost of the stapler suggest that the cost of the stapler would have to fall to zero for the difference in cost results to change in favour of SH. However, the cost-effectiveness results would lie in the segment of the south-west quadrant of the cost-effectiveness plane (SH would cost less than TH, but have fewer QALYs than TH) where the cost savings do not outweigh the associated QALY losses.

Strengths

A key strength of the study was that it was a multicentre study with centres across the UK that followed up participants for 24 months. In addition, it is the first RCT to compare SH with TH. The incorporation of a wider economic perspective on costs as a secondary analysis adds value in terms of a broader economic perspective and understanding of the non-health-care costs to participants, their families and the economy

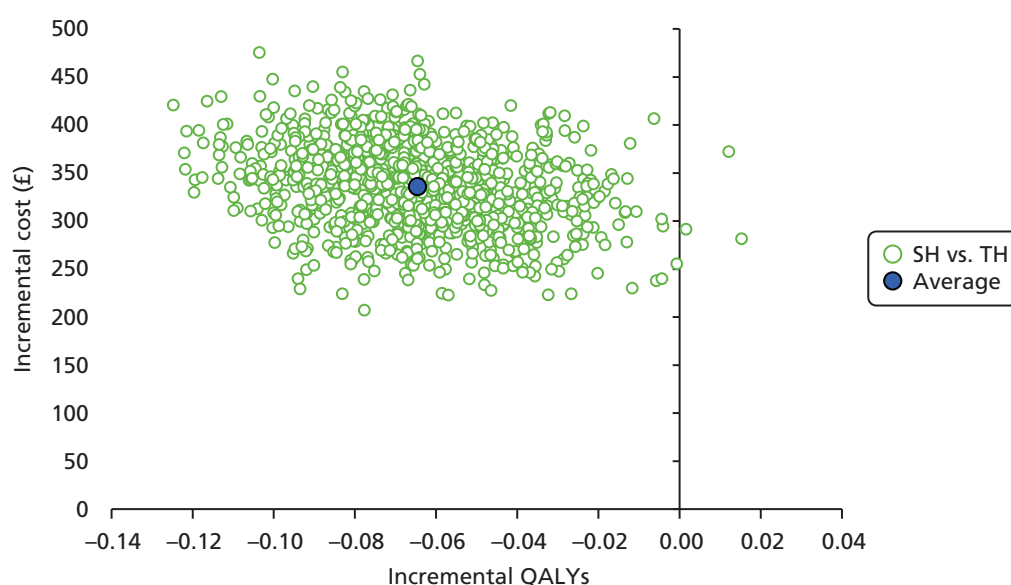


FIGURE 23 Cost-effectiveness scatterplot illustrating the distribution of cost and QALY differences as per sensitivity analysis: including societal costs.

more generally, of haemorrhoid symptoms and treatments. The analysis of QALYs based on EQ-5D-3L patient-level responses follows best practice and is another advantage. It is also reassuring that QALYs based on the alternative SF-6D instrument produce similar results.

Challenges

One of the challenges of the economic analysis was the number of missing data. Summaries of missing data indicated that the number of missing data was similar in both arms. MI methods that assumed the data to be missing at random were conducted to address this challenge. However, the results of the two analyses presented for imputed data set and complete case were similar, and the main conclusion remained the same irrespective of the approach.

Conclusion

The results of the within-trial analysis show that SH costs more and is less clinically effective than TH. These results were conclusive and supported by the sensitivity analyses and the fact that secondary outcomes such as tenesmus were more prevalent in the SH arm ($p < 0.001$), and more participants reported recurrence of haemorrhoids at both 12 and 24 months.

Chapter 7 Delivering person-centred care: what do the public and patients want (discrete choice experiment)

Background

Discrete choice experiments (DCEs) were introduced into health economics to value aspects of care beyond QALYs, and thus inform the delivery of public- and patient-centred care.^{47,48} Research funding programmes such as the NIHR HTA programme (UK)⁴⁹ are increasingly using applications of DCEs to assess what the public and patients want from the delivery of health care to inform key stakeholders such as policy-makers (NICE), researchers, NHS health professionals and the general public.

The DCE method can be used to assess the values of outcomes beyond QALYs in the delivery of treatment for haemorrhoids. Burch *et al.*² found that the outcomes of SH and TH differed in terms of short-term outcomes (earlier return to usual activities, pain) and the risk of recurrence. There was some concern that the recommended quality-of-life measurement (and QALYs based on it)²⁵ may not fully measure the change in quality of life, as it would not capture all the aspects that represent patients' preferences for treatments and their associated outcomes. The objectives of the DCE were to:

- investigate the outcomes of haemorrhoidal treatment that matter to individuals and their relative importance
- estimate the value of such outcomes using WTP, a monetary measure of value for outcomes
- compare costs and benefits in monetary terms, within a cost–benefit analysis framework, using this person and patient-centred measure of value
- compare the results from the standard cost–utility analysis approach (cost per QALY) with the cost–benefit analysis results.

The DCE included an additional surgical intervention, HAL, to take into account all the treatment options currently available to patients with haemorrhoids (and considered within the study).

Methods

Developing the discrete choice experiment

Discrete choice experiments involve four stages: (1) identification of attributes and levels; (2) questionnaire development; (3) data collection; and (4) data analysis and interpretation.^{50,51}

Stage 1: identification of attributes and levels

The first stage is to define the attributes or factors important in the treatment of haemorrhoids. The attributes, derived from a previous study² and expert advice, are shown in *Table 45*. *Time in postoperative pain* had an impact as it could last up to 4 weeks post surgery. *Chance of serious complications* took account of post-surgery effects such as skin tags, which can cause pruritus and difficulty with personal hygiene, and may need further intervention to remove. Other complications that could lead to hospitalisation, such as bleeding, wound and systemic infections, faecal and urinary incontinence, anal stenosis and anastomotic stricture, were also important. *Time taken to return to usual activities* would have an impact on patients, particularly those of working age. *Chance of recurrent prolapse* might lead to the need for further treatment. To allow the estimation of WTP for attributes, and thus monetary values of different treatments within a cost–benefit analysis framework, a *cost-of-treatment* attribute was included.

TABLE 45 Attributes and levels

Attribute and description	Level
Time in postoperative pain	
This describes the number of days in which you are in pain during the first 6 weeks after your operation. This is pain that requires taking painkillers for relief. For example, the pain may last for:	• 3 days • 7 days • 21 days • 30 days
Chance of serious complications requiring hospitalisation	
This refers to complications/side effects of the treatment that could lead to visiting a health-care provider, such as accident and emergency department visits or spending a few days in hospital. These complications could include severe bleeding/haemorrhage, abscess after operation, infection and urinary or faecal incontinence. For example, the chance might be that of:	• 10 in 1000 (1.0%) people • 15 in 1000 (1.5%) people • 20 in 1000 (2.0%) people • 30 in 1000 (3.0%) people
Time taken to return to usual activities	
This describes the time that it may take you to return to your usual activities, such as work, housekeeping, leisure or studying	• 3 days • 7 days • 21 days • 30 days
Chance of a recurrence of haemorrhoidal symptoms	
This describes the chance that in 12 months' time the symptoms you had before your surgery might come back. These symptoms include minor bleeding, itching, pain and skin tags	• 9 in 1000 (0.9%) people • 15 in 1000 (1.5%) people • 18 in 1000 (1.8%) people • 21 in 1000 (2.1%) people
Cost of treatment	
This refers to how much you would value the surgical interventions. One way of finding out the value is to find out how much you would be willing to pay for such a service. Please consider what you would be personally willing and able to pay for the service you choose. <u>Remember that any money you spend on this service will not be available to spend on other things</u>	• £100 cost per treatment • £200 cost per treatment • £300 cost per treatment • £400 cost per treatment

Levels for the attributes were derived from the study data and discussions with gastroenterology experts. Levels were anchored on the minimum and maximum number of days in pain postoperatively and time to return to usual activities, and the chance of serious complications or recurrence cited in the literature. Levels for the cost attribute were defined from a pre-pilot WTP survey (see *Table 45*).

Stage 2: questionnaire development

The five attributes and four levels yield 1024 possible profiles (5^5), too many to present to individuals. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used to develop a D-efficient fractional factorial design to reduce the profiles to a manageable level while still being able to infer utilities (or benefit) for all possible choices.⁵² The experimental design maximises the precision of estimated parameters (by maximising the D efficiency, a summary measure of the variance–covariance matrix) for a given number of choice sets. The design had 32 choice sets, which were randomly split into four questionnaires, each containing eight choice tasks (see *Appendix 1*). For each choice, respondents were asked to state which option they would choose: excisional (TH), artery ligation (HAL), stapled (SH) or no treatment. The no-treatment or opt-out alternative was included to reflect reality, as patients can choose not to be treated. An example of a choice set is shown in *Table 46*.

The questionnaire also contained a description of the DCE task, a description of the attributes and levels and an example of a completed choice set. Information was also collected on respondents' sex, age, income, health status (EQ-5D-3L) and experience of haemorrhoids.

TABLE 46 Example of a choice set

Attribute	Excisional	Artery ligation	Stapled	No treatment
Time (days) in postoperative pain	7	21	30	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	30 in 1000 people (3%)	10 in 1000 people (1%)	
Time (days) taken to return to usual activities	21	30	42	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	15 in 1000 people (1.5%)	18 in 1000 people (1.8%)	
Cost (£) of treatment	300	400	200	
Which would you choose (please tick one)	Excisional	Artery ligation	Stapled	No treatment
	☐	☐	☐	☐

Stage 3: respondent recruitment and data collection

An important consideration in preference elicitation is whose preferences to elicit.⁵³ Should it be the general population, whose resources are being allocated (and whose values are used for the EQ-5D-3L), or patients who have experience of the disease? If preferences differ across groups, making decisions based on one group's preferences may be suboptimal for the other. Therefore, patients who have the experience of both disease and treatment and the general population were considered appropriate for this study.

The patient sample was recruited from the study participants. A total of 293 study participants were sent a pen-and-paper questionnaire 24 months after treatment. The general population sample was recruited from members of a commercial online panel (Research Now).⁵⁴ Panel members were sent an e-mail inviting them to complete the online survey. The survey was pre-piloted among a small sample of the research group and the HSRU, University of Aberdeen, to refine all practical aspects of the survey, such as explanations and presentation of choices and to ensure that respondents were understanding and making trade-offs between the attributes. The pilot questionnaire was sent to 50 members of the online survey panel to ensure that respondents would trade and to ensure that the results were meaningful (with estimated parameters moving in the expected direction).

Stage 4: data analysis

The following model was used to analyse the responses:

$$\begin{aligned}
 U = & \beta_1(\text{TH}) + \beta_2(\text{HAL}) + \beta_3(\text{SH}) + \beta_4(\text{time in postoperative pain}) + \beta_5(\text{chance of serious complications}) \\
 & + \beta_6(\text{time taken to return to usual activities}) + \beta_7(\text{chance of recurrence of haemorrhoids}) \\
 & + \beta_8(\text{cost}),
 \end{aligned}
 \tag{2}$$

in which 'U' is the utility (or benefit) for a defined profile, given levels of each attribute.

The parameters β_1 to β_8 are the coefficients of the model to be estimated and their interpretation depends on their unit of measurement. Parameters β_1 to β_3 are the treatment options TH, HAL and SH, which are measured relative to no treatment. The coefficients β_4 to β_8 are continuous, indicating their relative importance, or weight, for a unit change such as a 1% change in chance of recurrence of haemorrhoidal symptom on utility.

The rate at which respondents are willing to trade between these attributes (i.e. how much of the attribute they are willing to give up for the improvements in other attributes), is shown by the ratio of the coefficients; for example, β_4 divided by $-\beta_6$ indicates how much longer respondents are willing to wait before returning to usual activities in order to have reduced days in postoperative pain. The trade-offs respondents make between the cost of haemorrhoids and other attributes represents respondents' WTP for (or their value of) a unit change in attribute level. The marginal WTP (mWTP) for a unit change in one of the attributes is estimated as:

$$\text{WTP} = (\beta_i / -\beta_{\text{cost of treatment}}). \quad (3)$$

For example, (β_4/β_8) is respondents' mWTP for reducing the time in postoperative pain by 1 day and (β_7/β_8) is respondents' WTP for reducing the risk of complications by 1%. The mWTP was estimated for all attribute levels, and CIs for these values were calculated using a parametric bootstrap with 1000 replications of the model.⁵⁵

Equation 2 was estimated using the mixed-logit regression model, using Stata. This model allows for unobserved preference heterogeneity (variation in preferences across the sample, meaning that preferences cannot be adequately represented by the sample mean). We allowed for preference heterogeneity with respect to TH, HAL and SH, and assumed a normal distribution. Statistically significant SDs provide evidence of preference heterogeneity.

Cost–benefit analysis

A cost–benefit analysis was undertaken to compare costs and benefits, in monetary terms, of the two treatment options valued within the trial: SH and TH. To estimate total WTP for a defined option (SH or TH treatment) mWTP values for all attributes were combined with the average levels for each attribute for each treatment option. Actual levels for attributes and average treatment costs were informed by the trial data. A net benefit (benefits minus costs) was generated for SH and TH.

Results

Respondent characteristics

Although 1394 individuals accessed the web-based survey, 364 respondents dropped out and seven declined to take part, resulting in 1010 respondents (77.5%) completing the online questionnaire. *Table 47* presents a summary of respondents' characteristics. The mean age was 46 years, 51% were male ($n = 511$) and 44% reported that they had experienced haemorrhoids ($n = 441$). The respondents had an average utility score of 0.84. Over half of respondents (61%) were in some form of employment and 70% had at least secondary school-level education. Respondents were evenly distributed across income groups.

Of the 293 questionnaires sent to the eTHoS study participants, 66% ($n = 193$) were returned. The mean age was 54 years old and 52% were male ($n = 101$). The respondents' average utility score was 0.88. Respondents were evenly distributed across income groups (*Table 47*).

Results: web-based sample

Over all of the choices presented in the web-based DCE, 32% were for TH treatment, 30% for HAL treatment, 31% for SH treatment and 7% for no treatment. Very few respondents chose no treatment (8%). *Table 48* reports the results of the DCE analyses.

The coefficients for treatment options (TH, 5.043; HAL, 4.995; and SH, 4.709) are all statistically significant and positive. This indicates that everything else being equal, respondents have a general preference for being treated over not being treated. However, the coefficients for TH, HAL and SH are not significantly different from each other, with CIs overlapping. This suggests that respondents did not distinguish between the three treatment options (everything else being equal).

TABLE 47 Participant characteristics

Participant characteristics	Respondents			
	Web-based survey, <i>n</i>	%	Study participants, <i>n</i>	%
Total sample size	1010	100	193	100
Sex				
Male	511	51	101	52
Female	499	49	92	47
Age (years)				
Mean (SD)	1010	46 (16)	193	54 (13)
Education				
1–4 O levels/CSEs/GCSEs (any grades)	188	19	7	4
NVQ/SVQ Level 1 or 2, GNVQ/GSVQ	94	9	11	6
≥ 5 O levels (passes)	253	25	10	5
Apprenticeship	39	4	3	2
≥ 2 A levels/VCE	217	21	1	1
NVQ/SVQ Level 3	113	11	16	8
Degree	400	40	19	10
Professional qualifications	169	17	34	18
Other qualifications	122	12	47	25
Foreign qualifications	12	1	6	3
No qualifications	34	3	30	16
Prefer not to say	12	1	6	3
Employment status in the last week				
Employee	497	49	60	33
Self-employed or freelance	122	12	1	1
On a government training scheme	6	1	10	5
Working alone or family's business	21	2	3	2
Away from work: ill, maternity leave, on holiday or temporarily laid off	17	2	0	0
Doing any other kind of paid work	16	2	68	37
Actively looking for a job	36	4	5	3
Unemployed	36	4	2	1
Retired	187	19	4	2
Student	56	6	18	10
Looking after home or family	82	8	0	0
Long-term sick or disabled	46	5	7	4
Other: please specify	8	1	6	3
Annual income				
Up to £5199 per year	70	6	6	3
£5200 and up to £10,399 per year	109	11	27	14

continued

TABLE 47 Participant characteristics (*continued*)

Participant characteristics	Respondents			
	Web-based survey, <i>n</i>	%	Study participants, <i>n</i>	%
£10,400 and up to £15,599 per year	114	11	22	12
£15,600 and up to £20,799 per year	107	11	28	15
£20,800 and up to £25,999 per year	112	11	17	9
£26,000 and up to £31,199 per year	91	9	13	7
£31,200 and up to £36,399 per year	68	7	9	5
£36,400 and up to £51,999 per year	107	10	19	10
£52,000 and above per year	109	11	12	6
Prefer not to say	123	13	36	19
Experienced haemorrhoids				
Yes	441	44	193	100
No	569	56	0	0
General health				
Mean EQ-5D score (SD)	1010	0.839 (0.023)	191	0.880 (0.19)
Study treatment allocation				
SH	NA	NA	93	48
TH	NA	NA	100	52

A level, Advanced level; CSE, Certificate of Secondary Education; GCSE, General Certificate of Secondary Education; GNVQ, General National Vocational Qualification; GSVQ, General Scottish Vocational Qualification; NA, not applicable; NVQ, National Vocational Qualification; O level, Ordinary level; SVQ, Scottish Vocational Qualification; VCE, Vocational Certificate of Education.

TABLE 48 Regression results for the general population

Attribute	Coefficient (95% CI)	Standard error	<i>p</i> -value
Mean preferences ^a			
TH	5.043 (4.802 to 5.284)	0.123	< 0.001
HAL	4.995 (4.761 to 5.228)	0.119	< 0.001
SH	4.709 (4.482 to 4.936)	0.116	< 0.001
Time in postoperative pain	−0.043 (−0.046 to −0.040)	0.002	< 0.001
Chance of serious complications requiring hospitalisation	−0.369 (−0.411 to −0.326)	0.022	< 0.001
Time taken to return to usual activities	−0.030 (−0.033 to −0.028)	0.001	< 0.001
Chance of a recurrence of haemorrhoidal symptoms	−0.030 (−0.033 to −0.028)	0.001	< 0.001
Cost of treatment	−0.568 (−0.636 to −0.501)	0.034	< 0.001
Measures of variability in preferences (SD)			
TH	1.238 (1.118 to 1.359)	0.061	< 0.001
HAL	1.119 (1.005 to 1.233)	0.058	< 0.001
SH	1.248 (1.125 to 1.372)	0.063	< 0.001

^a Log-likelihood −9032; likelihood ratio chi-squared (3) = 863; number of individuals (1010), number of observations [32,320 (1010 individuals × 8 choices × 4 options per choice)].

The SDs for TH, SH and HAL (see the lower part of *Table 48*) are statistically significant, indicating preference heterogeneity for treatment options. Under the mixed-logit model assumptions in which TH, HAL and SH are normally distributed, these results still suggest that almost 100% of the population prefer treatment over no treatment. The coefficients for all the attributes are statistically significant and, as expected, negative. This indicates face validity for the model, with increases in all attributes reducing the utility and probability of take-up of a given treatment option. The magnitude of the coefficients show the impact of a unit change in the attribute. For example, a 1% increase in the chance of recurrence of haemorrhoids reduces utility by –0.568 and a 1% increase in chance of serious complications needing hospitalisation reduces utility by –0.369.

Willingness to pay: a monetary measure of value

Marginal WTP values are shown in *Table 49*. Respondents are willing to pay £1802 to move from no treatment to TH, £1785 to move to HAL and £1683 to move to SH. Although WTP is highest for TH, the values are not statistically significantly different. Everything else being equal, respondents were willing to pay £203 for a 1% reduction in the chance of recurrence of haemorrhoidal symptoms; £132 for a 1% reduction in the chance of serious complications requiring readmission; £15 for a 1-day reduction in time spent in postoperative pain; and £11 for a 1-day reduction in time taken to return to usual activities.

Results from eTHoS participants

The study participants' results were similar to those of the web-survey group (*Table 50*). All treatment attributes were significant at the 5% level, suggesting that they all influenced preferences for haemorrhoidal treatments. Although the cost attribute was negative, it was not statistically significant. It was therefore not possible to calculate WTP values for the trial participants.

Cost–benefit analysis

Table 51 shows the results of the cost–benefit analysis. Total WTP for the two treatment options, SH and TH, can be defined as:

$$\begin{aligned} \text{SH} = & 1683 + \text{mWTP} \times \text{days in postoperative pain} + \text{mWTP} \\ & \times \text{chance of serious complications requiring hospitalisation} + \text{mWTP} \\ & \times \text{days taken to return to usual activities} + \text{mWTP} \\ & \times \text{chance of serious recurrence of haemorrhoidal recurrence.} \end{aligned} \quad (4)$$

TABLE 49 Willingness to pay for attributes

Attribute	WTP (£) (95%CI)	Preference interpretation
TH	1802 (1636 to 1968)	Willing to pay £1802 to move from no treatment to TH
HAL	1785 (1623 to 1946)	Willing to pay £1785 to move from no treatment to HAL
SH	1683 (1533 to 1833)	Willing to pay £1683 to move from no treatment to SH
Time in postoperative pain	–15 (–17 to –13)	If time increases by 1 day, then WTP decreases by £15
Chance of serious complications requiring hospitalisation	–132 (–151 to –112)	If risk increases by 1%, then WTP decreases by £132
Time taken to return to usual activities	–11 (–12 to –9)	If time increases by 1 day, then WTP decreases by £11
Chance of a recurrence of haemorrhoidal symptoms	–203 (–233 to –173)	If risk increases by 1%, then WTP decreases by £203

TABLE 50 Regression results for the eTHoS study participants

Attribute	Coefficient (95% CI)	<i>p</i> > <i>z</i>
Mean preferences		
TH ^a	7.173 (6.300 to 8.046)	<i>p</i> < 0.001
HAL	6.669 (5.881 to 7.457)	<i>p</i> < 0.001
SH	7.029 (6.222 to 7.837)	<i>p</i> < 0.001
Time in postoperative pain	−0.047 (−0.056 to −0.038)	<i>p</i> < 0.001
Chance of serious complications requiring hospitalisation	−0.520 (−0.642 to −0.397)	<i>p</i> < 0.001
Time taken to return to usual activities	−0.036 (−0.043 to −0.029)	<i>p</i> < 0.001
Chance of a recurrence of haemorrhoidal symptoms	−1.175 (−1.373 to −0.977)	<i>p</i> < 0.001
Cost of treatment	0.000 (−0.001 to 0.001)	0.776
Measures of variability in preferences (SD)		
TH	2.271 (1.737 to 2.805)	<i>p</i> < 0.001
HAL	1.934 (1.438 to 2.430)	<i>p</i> < 0.001
SH	2.180 (1.636 to 2.723)	<i>p</i> < 0.001

a Log-likelihood −1278; LR chi-squared (3) = 578; number of individuals (193), number of observations [5824 (193 individuals × 8 choices × 4 options per choice)].

TABLE 51 Net benefit analysis

Parameters used to estimate net benefit	WTP (DCE)	Trial arm (study outcome)	
		SH	TH
SH	£1683	–	–
TH	£1802	–	–
Time in postoperative pain	−£15	8.14 days	8.92 days
Chance of serious complications requiring hospitalisation	−£132	0.25	0.30
Time taken to return to usual activities	−£11	15.47 days	19.05 days
Chance of a recurrence of haemorrhoidal symptoms	−£203	0.42	0.25
Total WTP	–	£1271	£1367
Cost from study	–	£941	£602
Net benefit ^a	–	£330	£765

a Net benefit was calculated as the WTP at 24 months using general population DCE data and study outcomes.

$$SH = 1683 + (-15 \times 8.14) + (-132 \times 0.25) + (-11 \times 15.47) + (-203 \times 0.42). \quad (5)$$

$$\begin{aligned} TH = & 1802 + \text{mWTP} \times \text{days in postoperative pain} + \text{mWTP} \\ & \times \text{chance of serious complications requiring hospitalisation} + \text{mWTP} \\ & \times \text{days taken to return to usual activities} + \text{mWTP} \\ & \times \text{chance of serious recurrence of haemorrhoidal recurrence}. \end{aligned} \quad (6)$$

$$TH = 1802 + (-15 \times 8.92) + (-132 \times 0.30) + (-11 \times 19.05) + (-203 \times 0.25). \quad (7)$$

While the total WTP estimates were positive for both treatments (£1277 and £1367, SH and TH, respectively), the net benefit was higher for TH than SH (£765 vs. £330).

Discussion

Following the standard approach to valuation in trials (costs per QALY), we estimated a broader measure of value using the DCE. Following this, we generated a monetary measure of value that took account of factors important to users in the delivery of treatments for haemorrhoids (for the general population). Overall, respondents in both groups had a general preference to have treatment over no treatment, but did not distinguish between the three treatment options. However, they also had preferences for the attributes identified, with decreases in all four treatment attributes, as expected, reducing the benefit of treatment. The magnitude of coefficients indicated that the most important marginal change was chance of recurrence, followed by chance of complications.

An interesting finding was that cost was not significant to study participants. This may be explained by study participants having experienced treatment at zero cost to them (at the point of consumption). If DCEs are to be used to estimate a broader measure of value, this raises questions regarding who should complete the DCE and when. We leave this to future research.

The results of the within-study analysis reported in *Chapter 6* suggested that the EQ-5D-3L captured differences in quality of life, and that TH costs less (–£337) and is associated with more (0.07) QALYs than SH. The standard cost–utility analysis thus suggested TH as the optimal treatment. These cost–utility analysis results were confirmed by the cost–benefit analysis, which indicated that TH had a higher INB.

Conclusions

Respondents from both the general population and the trial participants valued aspects of treatment beyond those captured in the QALYs. Respondents across groups also had similar preferences for treatment attributes. New haemorrhoidal treatments should aim at reducing the chance of recurrence and complications, as well as the time in postoperative pain and time taken to return to usual activities. The cost–benefit analysis results suggesting TH as the optimal treatment concur with the cost-per-QALY results.

Chapter 8 Use of monetary incentives to boost participant questionnaire response rates in the eTHoS study: the 'to incentivise or not to incentivise' studies

Introduction

Response rates to the questionnaires administered at follow-up in the eTHoS study were routinely monitored at monthly in-house team meetings. Although response rates to the two early questionnaires were acceptable, there was no further contact with participants until the 12-month follow-up questionnaire and no contact between the 12- and 24-month questionnaires. The response rate to the 12-month follow-up questionnaire was observed to be lower than expected part way through the recruitment period. Options to improve the response rates were therefore considered by the study team. Literature reviews looking at methods to increase response rates were reviewed, and it was found that monetary incentives were likely to increase response rates.⁵⁶ However, there was limited evidence from studies in the UK and RCTs. It was therefore decided to conduct a formal evaluation of whether or not using a monetary incentive improved the response rate. This study was called 'to incentivise or not to incentivise' (IONTI). Surprisingly, the response rates continued to be low, and a need to protect the response rates in the main study was paramount; hence, the IONTI study was stopped early after 15 months. Subsequently, after a further review of the literature, a second incentive approach was implemented and its impact was assessed in the IONTI-2 study. The background, design and findings from both of these 'studies within a trial' (SWATs) are described in this chapter. *Appendix 4* gives an overview of the timeline for both the IONTI and IONTI-2 studies.

'To incentivise or not to incentivise'

In early 2013, the response rates to the 12-month follow-up questionnaire were found to be lower than expected at 69% (97/140 as of 25 February 2013); the expected response rate was 85%. Following discussion at the PMG meeting on 26 March 2013, it was decided that action needed to be taken in order to increase the response rate as much as possible. In order to choose the most effective intervention to increase the follow-up response rates in the eTHoS study, the team turned to the literature. A review published by The Cochrane Library⁵⁶ evaluating strategies to boost response rates looked at 110 different strategies in 481 trials using postal questionnaires and 27 different strategies in 32 trials using electronic questionnaires. Although the eTHoS study follow-up data were collected using self-report by postal and electronic means, the largest proportion of responses were postal and, therefore, this mode of administration was also prioritised when designing the SWAT.

The literature review showed that in postal but not electronic questionnaire studies, monetary incentives were suggested to be the most likely to be effective in increasing response rates (OR 1.87, 95% CI 1.73 to 2.04), although there was significant heterogeneity among results.⁵⁶ The amount of the incentive might also affect the impact of monetary incentives. The review showed that in the 37 studies included, in which larger and smaller monetary incentives were compared, larger amounts were more effective. A further variation in studies using monetary incentives is whether the incentive is conditional or unconditional, that is, whether or not a voucher can be forwarded on the condition that the participant returns a completed questionnaire, or the voucher can be sent with the questionnaire to be completed and the participant does not have to do anything before receiving it. The review found that unconditional monetary incentives were more effective than conditional monetary incentives. However, very few studies used gift vouchers, few were clinical trials and only a small number were carried out in the UK; therefore, the generalisability of the findings could be questioned.

One study carried out, in the UK, by Gates *et al.*⁵⁷ showed a positive impact on response rates following the introduction of a monetary incentive, a £5 gift voucher, into their RCT on advice for whiplash patients. Participants ($n = 2144$) were randomised to two groups: one group received a gift voucher at both follow-up points and the other group did not receive any incentive. Participants in the former group ($n = 1070$) received the gift voucher unconditionally with their questionnaire at the 4- and 8-month follow-up points. The results showed that the incentive group was more likely to return the questionnaires (relative risk 1.10, 95% CI 1.05 to 1.16), an absolute increase of 7% of questionnaires returned. However, the authors acknowledged that further research was needed in order to establish whether or not the findings were generalisable to different populations and different types of trials.

In addition, the eTHoS study also presented an opportunity to assess the introduction of an incentive part way through a study to address the lower than anticipated response rate to a postal questionnaire; this is a scenario that trialists regularly face. Further steps were also taken in order to protect the response rate of the main study during the IONTI study; however, these were not randomised.

Based on the limited evidence available, the eTHoS study team decided to conduct a SWAT looking at the impact of an unconditional and, therefore, small £5 high-street gift voucher on questionnaire response rates at the 12- and 24-month follow-up points, and whether or not the timing of the incentive has an impact. The specific research questions are explored in detail in the following sections.

Aim

The overall aim was to assess whether or not sending an unconditional £5 high-street gift voucher improves the response rate to the 12- and 24-month patient questionnaires.

The specific research questions were as follows.

1. Does sending an unconditional £5 high-street gift voucher with the 12-month follow-up questionnaire improve the response rate to this questionnaire?
2. Does sending an unconditional £5 high-street gift voucher with the 24-month follow-up questionnaire improve the response rate to this questionnaire?
3. Is there any indication of an interaction when a £5 high-street gift voucher is sent at 12 and 24 months?

Methods: 'to incentivise or not to incentivise'

Participants/eligibility

As of 5 June 2013, patients enrolled in the eTHoS study, across all clinical sites, who had yet to receive their 12- and 24-month follow-up questionnaires, were randomised into one of four groups described in Table 52.

TABLE 52 Description of the four participant groups in the IONTI study

Follow-up time point	Group			
	1	2	3	4
12-month follow-up	Voucher	Voucher	No voucher	No voucher
24-month follow-up	No voucher	Voucher	Voucher	No voucher

Materials

All participants who were randomised to receive a voucher were sent a covering letter describing the purpose of the 12- or 24-month follow-up questionnaire and why a voucher was included (see *Appendix 4*).

The IONTI study participants received the same standard 12- and 24-month follow-up questionnaires as described in *Chapter 3*, and the same reminders (postal then telephone reminders).

A £5 Love2Shop (Park Group plc, London, UK) voucher was included with the postal questionnaire according to group allocation. This brand of vouchers was chosen as they would be accepted in a range of high-street shops across the UK and should therefore be convenient to use for all participants.

Randomisation

Simple randomisation (1 : 1 : 1 : 1) was completed to allocate the eTHoS study participants to one of the four groups.

NHS research ethics and other permissions

Ethics approval was sought for the IONTI study and submitted as a substantial amendment to the main study. Ethics approval was received on 25 April 2013 for amendment 16 of the REC reference number 10/S0802/17.

Sites also had to approve the IONTI study. Sites were informed about the IONTI study as standard practice for all substantial amendments and had 35 days of submission to object to the amendment, otherwise approval would be assumed.

One of the co-sponsors (University of Aberdeen) required a statement regarding the possible tax implications to be included in the IONTI study questionnaire cover letters. This was included as of June 2013. However, this was removed in April 2014, as the sponsor reviewed its guidelines for this statement to be applicable only to amounts exceeding £10.

Primary outcomes

The primary outcome was the response rates at 12 and 24 months for the four groups.

In addition, through the routine study management system, the following information was collected: date questionnaire sent, if a reminder was sent and date sent, if a second reminder was sent and date sent, if a response was received along with mode utilised (postal or online) and date of receipt.

Statistical analysis

The response rates to questionnaires at 12 and 24 months between the incentive and the non-incentive groups were compared using logistic regression. Two separate analyses were carried out, one each for the return of the 12- and 24-month questionnaires. For the analysis of return of the 12-month questionnaire, only a 12-month incentive main effect was included. The analysis of return of the 24-month questionnaire included both a 12-month and a 24-month incentive main effect. The possibility of an interaction was explored using an additional incentive at 12 months by incentive at 24-month interaction effect. Models were adjusted for the minimisation variables (sex, baseline EQ-5D-3L score, haemorrhoid grade and centre) and 95% CIs are reported.

In addition, a non-randomised comparison of the impact of the IONTI study on the response rates was completed. This was also analysed using logistic regression with the IONTI study viewed as a single intervention (ignoring each individual's randomised allocation) with the pre- and post-IONTI study responses compared.

Estimated sample size

A total of 600 participants were anticipated to be recruited or still to have 12-month questionnaires sent by 1 May 2013, and could potentially have been included in the IONTI study subject to approval and implementation. A sample of 300 per group would have allowed a difference of 10% (70–80%) to be detected with 80% statistical power at the two-sided 5% significance level. Seventy per cent was the estimated proportion, as of February 2013, of participants returning their 12-month questionnaire. The 24-month level was uncertain, given the low numbers that had reached that time point.

Stopping rules

If the monetary incentive was found to be effective, the IONTI study would be stopped and all participants due a 12- or 24-month follow-up questionnaire would receive a voucher. The possibility of the IONTI study being detrimental was not considered and a date for interim analysis was not set.

Study within a trial registration

The SWAT was registered on the SWAT repository store held by the Northern Ireland hub for Trials Methodology Research [this was referenced as SWAT13 Jonathan Cook (2013 February 01 1237)].

Other initiatives taken to improve response rates in the main study

As of September 2013, the effectiveness of the reminders was reviewed by the study team. Telephone reminders for 12 and 24 months were found to be ineffective and expensive. For this reason, the second reminder was changed to a postal reminder.

As of December 2013, both reminders for the 12- and 24-month questionnaires were shortened to contain only the primary outcome measure (EQ-5D-3L). The second shortened reminder (EQ-5D-3L) was also introduced at this time to replace telephone call reminders, and was to be sent at 18 months, replacing the participant travel cost questionnaire, which was now postponed to be sent after the 24-month follow-up questionnaire at 27 months.

As of May 2014, a newsletter was sent to participants 1 week before their 12- or 24-month follow-up questionnaires, highlighting that they would soon, approximately 1 week later, receive their next follow-up questionnaire. Participants who had completed their follow-up received a version of the newsletter without a pre-notification.

Results

Two sites did not approve the amendment for the IONTI study and, therefore, participants from 27 sites were eligible and randomised in the IONTI study. One site objected because of the possibility that participants' confidentiality might be breached as the sponsor is legally required to share details of individuals who have received payments if requested by HM Revenue & Customs, whereas the other site objected on ethical grounds.

In addition, one participant who was randomised to receive the voucher returned it, as he felt that as he did not receive surgical treatment, he was not eligible to receive the voucher.

Flow of participants

Figure 24 shows the flow of participants who were included in the IONTI study. There were 142 participants randomised to group 1 (voucher at 12 months but not at 24 months); 124 participants randomised to group 2 (voucher at 12 and 24 months); 123 randomised to group 3 (no voucher at 12 months but voucher at 24 months); and 132 participants randomised to group 4 (no voucher at 12 or 24 months). In total, 25 participants withdrew by the end of the study and one had died (unrelated). Baseline data are shown in Table 53.

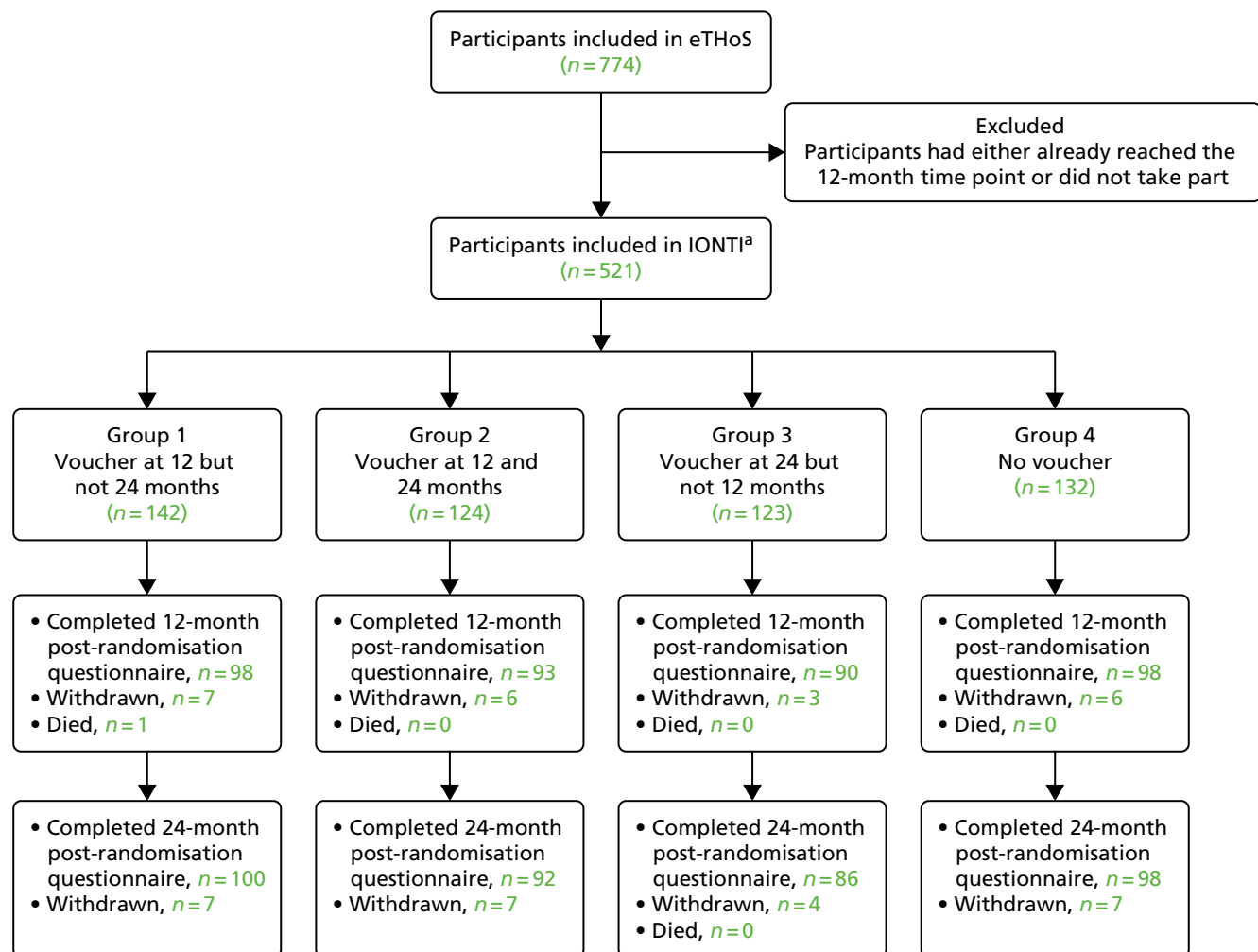


FIGURE 24 Flow of participants in the IONTI study. a, Participants eligible while the IONTI study was running from June 2013 until it was stopped in October 2014. Withdrawal refers to withdrawal from main study.

TABLE 53 Baseline characteristics for participants in the IONTI study

Characteristic	Trial arm			
	No voucher (N = 132)	12 months only (N = 142)	24 months only (N = 123)	Both time points (N = 124)
Age (years), <i>n</i> , median (IQR)	132, 50 (40–59)	142, 48 (38–58)	123, 50 (41–60)	124, 50 (42–61)
Sex (male), <i>n</i> (%)	62 (47.0)	73 (51.4)	64 (52.0)	63 (50.8)
BMI, <i>n</i> , mean (SD)	127, 26.8 (4.9)	137, 27.7 (5.2)	121, 26.6 (5.0)	120, 27.1 (5.3)
Grade of haemorrhoid, <i>n</i> (%)				
II	27 (20.5)	37 (26.1)	27 (22.0)	26 (21.0)
III	85 (64.4)	83 (58.5)	81 (65.9)	78 (62.9)
IV	20 (15.2)	22 (15.5)	15 (12.2)	20 (16.1)
Previous haemorrhoid surgery, <i>n</i> (%)	37 (28.0)	52 (36.6)	45 (36.6)	31 (25.0)
Comorbidities, <i>n</i> (%)	1 (0.8)	–	2 (1.6)	2 (1.6)
Systemic medications, <i>n</i> (%)				
Aspirin	7 (5.3)	1 (0.7)	7 (5.7)	7 (5.6)
Warfarin	2 (1.5)	1 (0.7)	1 (0.8)	1 (0.8)
Clopidogrel	2 (1.5)	1 (0.7)	4 (3.3)	2 (1.6)
Steroids	–	2 (1.4)	1 (0.8)	–
Other	3 (2.3)	–	1 (0.8)	1 (0.8)
Pain (VAS), <i>n</i> , mean (SD)	131, 2.6 (2.4)	140, 3.0 (2.5)	121, 2.4 (2.7)	121, 2.8 (2.9)
Analgesia, <i>n</i> (%)				
Yes	42 (31.8)	44 (31.0)	40 (32.5)	37 (29.8)
Missing	1 (0.8)	1 (0.7)	3 (2.4)	2 (1.6)
Number of days in a week with analgesia, <i>n</i> , mean (SD)	42, 3.8 (2.0)	44, 4.3 (2.2)	40, 5.1 (2.2)	36, 4.4 (2.1)
EQ-5D-3L, <i>n</i> , mean (SD)	132, 0.812 (0.216)	142, 0.735 (0.264)	123, 0.771 (0.262)	124, 0.751 (0.266)
SF-36, <i>n</i> , mean (SD)				
Physical component summary	130, 49.6 (9.3)	139, 48.5 (9.5)	119, 48.3 (10.0)	124, 48.3 (10.4)
Mental component summary	130, 50.4 (10.1)	139, 49.1 (11.1)	119, 50.2 (11.7)	124, 47.9 (12.3)
CIS, <i>n</i> , mean (SD)	129, 3.9 (3.6)	137, 4.5 (3.7)	118, 3.4 (3.7)	120, 4.6 (4.5)
HSS, <i>n</i> , mean (SD)	129, 12.9 (3.7)	134, 12.5 (3.9)	116, 12.5 (3.7)	120, 12.5 (4.3)
Patient reporting tenesmus, <i>n</i> (%)				
Always	2 (1.5)	6 (4.2)	4 (3.3)	3 (2.4)
Often	18 (13.6)	18 (12.7)	14 (11.4)	14 (11.3)
Sometimes	36 (27.3)	36 (25.4)	33 (26.8)	28 (22.6)
Rarely	19 (14.4)	30 (21.1)	17 (13.8)	19 (15.3)
Never	57 (43.2)	51 (35.9)	50 (40.7)	60 (48.4)
Missing	–	1 (0.7)	5 (4.1)	–

TABLE 53 Baseline characteristics for participants in the IONTI study (*continued*)

Characteristic	Trial arm			
	No voucher (N = 132)	12 months only (N = 142)	24 months only (N = 123)	Both time points (N = 124)
Patient preference, n (%)				
Strongly prefer better short-term recovery	11 (8.3)	12 (8.5)	11 (8.9)	10 (8.1)
Prefer better short-term recovery	11 (8.3)	11 (7.7)	6 (4.9)	3 (2.4)
No preference	42 (31.8)	57 (40.1)	51 (41.5)	47 (37.9)
Prefer lower risk of recurrence	33 (25.0)	38 (26.8)	28 (22.8)	28 (22.6)
Strongly prefer lower risk recurrence	35 (26.5)	23 (16.2)	24 (19.5)	34 (27.4)
Missing	–	1 (0.7)	3 (2.4)	2 (1.6)
BMI, body mass index.				

In general, the groups were well balanced. *Table 54* provides the IONTI study response rate results. There were no statistically significant differences between the groups at 12 or 24 months. Similarly, there was no evidence of an interaction effect (*Tables 55 and 56*).

TABLE 54 The IONTI study: responses to questionnaires at 12 and 24 months

Response time point	Time point of voucher, n (%)			
	12 months		24 months	
	No	Yes	No	Yes
Response at 12 months				
No	62 (24.3)	69 (25.9)	–	–
Yes	193 (75.7)	197 (74.1)	–	–
Response at 24 months				
No	71 (27.8)	74 (27.8)	76 (27.7)	69 (27.9)
Yes	184 (72.2)	192 (72.2)	198 (72.3)	178 (72.1)

TABLE 55 The IONTI study: ORs of responses to questionnaires at 12 and 24 months

Response time point	OR (95% CI)	p-value
Response at 12 months		
Voucher at 12 months	0.99 (0.72 to 1.37)	0.962
Response at 24 months		
Voucher at 12 months	0.93 (0.60 to 1.44)	0.760
Voucher at 24 months	0.85 (0.48 to 1.52)	0.586
Interaction	1.39 (0.69 to 2.79)	0.358

TABLE 56 The IONTI study: before-and-after analysis to response to questionnaires at 12 and 24 months

Time point post randomisation	Responded to questionnaire, <i>n</i> (%)		OR (95% CI)	<i>p</i> -value
	Yes	No		
12 months				
Before	178 (72.1)	69 (27.9)	–	–
After	408 (77.4)	119 (22.6)	1.31 (0.84 to 2.04)	0.237
24 months				
Before	30 (71.4)	12 (28.6)	–	–
After	532 (72.7)	200 (27.3)	1.01 (0.55 to 1.86)	0.980

The ‘to incentivise or not to incentivise’-2 study

Response rates remained lower, at 75% (375/498) for the 12-month questionnaire and 60% (127/212) for the 24-month questionnaire, than the expected rate of 85%, despite the fact that the IONTI study ran for 1 year. The eTHoS study team turned to the literature again for guidance.

A systematic literature review suggested that higher-value incentives were effective in increasing response rates to postal questionnaires in randomised trials. In their review, Brueton *et al.*⁵⁸ looked at randomised SWATs that compared strategies with increase response rates to follow-up questionnaires in RCTs. They identified 38 eligible SWATs, of which 14 tested incentives and two compared size of incentive. The two trials ($n = 902$) showed that those receiving a higher-value incentive were more likely to respond to questionnaires than those who received lower-value incentives (relative risk 1.12, 95% CI 1.04 to 1.22; $p < 0.005$), irrespective of how the incentive was delivered.

Based on the evidence reviewed above, the study team decided to conduct another monetary incentive study, IONTI-2. In the IONTI-2 study a high-value gift voucher (£30) was sent to participants who returned a fully completed 12- or 24-month questionnaire or associated reminders. A fully completed questionnaire was defined as one in which the primary outcome measure, the EQ-5D-3L, was completed.

Aim

The aim of the IONTI-2 study was to investigate the impact of a conditional £30 gift voucher on response rates at the 12- and 24-month follow-up points.

Methods: the ‘to incentivise or not to incentivise’-2 study

Participants/eligibility

As of 17 October 2014, patients enrolled in the eTHoS study across all clinical sites, who had yet to receive their 1-year and/or 2-year follow-up questionnaire, were eligible.

Materials

All participants received a covering letter describing the purpose of the 12- or 24-month follow-up questionnaire and were informed that on return of a completed questionnaire they would receive a £30 gift voucher as a token of appreciation for their time spent completing the questionnaire (see *Appendix 4*).

The IONTI-2 participants received the same standard 12- and 24-month follow-up questionnaires as described in *Chapter 3*, and the same reminders (by this time amended to two postal reminders containing only the EQ-5D-3L, and an 18-month reminder if no return at 12 months).

On receipt of a completed questionnaire (12- or 24-month questionnaire reminders or 18-month reminder), the primary outcome measure had to be completed, a £30 gift voucher was triggered and sent to the participant.

The Love2Shop brand of vouchers was chosen as these would be accepted in a range of high-street shops across the UK and should therefore be convenient to use for all participants.

As of 21 January 2015 a label was added to the front of questionnaires, giving participants a choice to opt out from receiving the gift voucher (see *Appendix 4*). The team felt that this option should be made available for participants who were taking part in the study solely for altruistic reasons.

NHS research ethics and other permissions

Ethics approval was sought for the IONTI-2 study and a substantial amendment was submitted to the main study. Ethics approval was received on 8 September 2014 for amendment 27 for REC reference number 10/S0802/17.

Sites also had to approve the IONTI-2 study. Sites were informed about the IONTI-2 study as standard practice for all substantial amendments and could object within 35 days of submission of the amendment, otherwise approval would be assumed.

As vouchers had a value of more than £10, the sponsor required a statement regarding the possible tax implications to be included with the vouchers. A compliment slip was included in the mailing with the voucher informing participants of possible tax implications (see *Appendix 4*).

Primary outcomes

The main primary outcome was response rates at 12 and 24 months for participants included in the IONTI-2 study.

In addition, through the routine study management system, the following information was collected: date questionnaire was sent, if a reminder was sent and date sent, if a second reminder was sent and date sent, if a response was received along with mode utilised (postal or online) and date of receipt.

Statistical analysis

The primary analysis was a before-and-after analysis of the impact of the £30 gift voucher at 12 and/or 24 months using logistic regression with adjustment for the minimisation variables. The primary analysis included all participants who had not already reached the 12- and/or 24-month time point.

A further analysis using the preceding IONTI study period data along with all of the data up to the end of the 24-month follow-up period was carried out.

A post hoc sensitivity analysis was carried out as a result of the overlapping influence of the IONTI study. For the 12-month analysis, this included participants not included in the IONTI-2 study, participants who were randomised to no voucher and those who received the voucher at 24 months only. For the 24-month analysis, this included participants not included in the IONTI-2 study and participants who were randomised to receive no vouchers in the IONTI-2 study. Data on responses were collected and compared.

One interim analysis for futility was planned once the outcome for 75% of the anticipated participants in the IONTI-2 study was known at 24 months. Based on this, it was decided to continue the study to completion.

Owing to a system error, the shortened reminders (introduced in December 2013) were not issued to participants at 24 months for a period of 12 months during the IONTI study. This might have impacted on the response rate at 24 months. To protect the host study, eTHoS, these missed 24-month reminders were sent out during the IONTI-2 study and these included the conditional voucher incentive to maximise response rates. These returned reminders were not included in the final analysis for the IONTI-2 study.

Estimated sample size

A total of 440 recruits were anticipated to still be due to receive their 24-month questionnaires at the time of design. Based on a simple pre–post comparison of the return rate, a sample of 216 per group would allow a difference of 16% (60–75%) to be detected with 90% statistical power at the two-sided 5% significance level. This may be reduced slightly because of the single interim analysis, although it is anticipated to be over 80%.

Study within a trial registration

The SWAT was registered on the SWAT repository store held by the Northern Ireland hub for Trials Methodology Research [reference: SWAT13 Jonathan Cook (2013 February 01 1237)].

Other initiatives taken to improve the response rates in the main study

No new steps were taken during the IONTI-2 study.

Results

'To incentivise or not to incentivise'-2

All sites agreed to take part in the IONTI-2 study. The IONTI-2 study began on 17 October 2014 when the IONTI study ceased. A total of 5% of participants (24/481) who completed the questionnaire opted not to receive the voucher. *Table 57* provides the IONTI-2 study results, which showed no statistical evidence of a change in the response rate.

Owing to the different follow-up points that individuals were at in that point in time, a small proportion of participants took part in both SWATs – 'a middle group'. *Table 58* provides the IONTI-2 sensitivity analyses results, exploring this 'middle group'. There was no evidence of a difference in the 12-month response rates after the incentive was given. This was also the same at 24 months, but there was a slight increase in response rates (71.4% before the incentive, 75.9% after the incentive).

TABLE 57 The IONTI-2 study: full dataset

Time point post randomisation	Responded to questionnaire, <i>n</i> (%)		OR (95% CI)	<i>p</i> -value
	Yes	No		
12 months				
Before	443 (75.1)	147 (24.9)	–	–
After	143 (77.7)	41 (22.3)	1.13 (0.75 to 1.69)	0.559
24 months				
Before	205 (69.3)	91 (30.7)	–	–
After	357 (74.7)	121 (25.3)	1.31 (0.97 to 1.76)	0.074

TABLE 58 The IONTI-2 study: sensitivity analysis

Time point post randomisation	Responded to questionnaire, <i>n</i> (%)		OR (95% CI)	<i>p</i> -value
	Yes	No		
12 months				
Before	434 (77.1)	129 (22.9)	–	–
After	143 (77.7)	41 (22.3)	1.01 (0.66 to 1.55)	0.974
24 months				
Before	205 (71.4)	82 (28.6)	–	–
After	349 (75.9)	111 (24.1)	1.25 (0.87 to 1.80)	0.230

Discussion

Findings from the IONTI and IONTI-2 studies were inconclusive with regard to the overall question. The IONTI study was stopped early as a result of concerns that it was having a negative impact on retention, based on anecdotal information and interim results. The overall response rates for the main study (eTHoS) were prioritised over the value of continuing the IONTI study. Findings from the IONTI study were statistically inconclusive. The overall analysis of IONTI-2 was similarly inconclusive, including the sensitivity analysis, which might be viewed as the purer analysis (excluding the group that had received an incentive in the IONTI study), which also showed no difference in response rate at 12 months. The 24-month finding was also statistically significant, but there was a slightly higher post-incentive response rate in both analyses.

As both SWATs were found not to be effective, the cost of these incentives per participant has not been calculated.

Taken together, the findings were, at best, inconclusive, and, from the study team's perspective, clearly disappointing. No positive effect was observed and there was the suspicion and possibility of a negative impact, despite previous work evaluating incentives as being very favourable.^{56,58} It is possible, however, that the negative finding here was only a chance finding. Alternatively, they could reflect something specific to the study and the way in which the incentives were delivered. There are a number of possible contributing factors. Of particular note was the requirement of the sponsor to include a statement in the covering letter regarding possible tax implications in the IONTI study. Anecdotal feedback from participants suggested that this caused concern to some participants. This institutional judgement was later revised on appeal, and the cover letter used was modified accordingly most of the way through the IONTI study intervention period. The eTHoS study participants received multiple questionnaires early in the follow-up period with a number of similar outcomes, which may have resulted in lower response rates. Introducing a relatively low-value incentive at 12 or 24 months might be viewed as too little and/or too late. It was later hoped that the study team could carry out qualitative research to fully explore the cause of the negative impact. This was not followed through, because of the substantial regulatory barriers and lack of resources. Further research in this area is recommended, preferably in a variety of settings to allow disease- and population-specific cohorts, along with features of follow-up, to be explored.

Multiple strategies to improve recruitment and response rate are regularly used in multicentre trials in which recruitment and/or response rates are lower than hoped. Often these are used without much evidence to support their use. It was the investigators' expectation at the initiation of the IONTI study that the use of incentives could be only positive (or, at worst, that they would have no impact). The findings from the IONTI studies question this assumption and points to the need for care when introducing new interventions part way through a study. Bower *et al.*⁵⁹ suggested that SWATs or 'nested' trials are needed to test the

effectiveness of retention strategies. However, triallists should be aware of the challenges of implementing SWATs part way through pragmatic trials. As noted by others in Glidewell *et al.*,⁶⁰ 'Interventions to increase response rates may incur negative consequences' contrary to the intuitive expectation.

Both studies had a number of limitations in terms of the evaluation of an intervention. A confounding factor during the conduct of the IONTI study was the use of pre-notification newsletters, which were also employed as a method to boost retention. There is some limited evidence that these are beneficial to boosting response rates.⁵⁶ Newsletters were issued 1 week prior to the 12- and 24-month questionnaire being distributed across all IONTI study groups; as such, it was not possible to untangle what impact this would have had upon the overall study. The IONTI and IONTI-2 studies were carried out in a fully 'open' manner, with the interim results monitored as part of the routine study management process by the study team. This reflected their primary aim to address the lower-than-anticipated response rate, with the main study being the priority. The decision to stop the study was not according to a prespecified stopping rule, but a corporate judgement of the study team. As such, this monitoring process increased the possibility of a misleading finding.

The IONTI-2 study had a number of limitations. As a before-and-after study, its findings are susceptible to secular trends and other concurrent changes. In particular, some participants were involved in both studies, 'a middle group', which makes the interpretation more difficult. We carried out a sensitivity analysis that excluded this group; however, such exclusion of data is not without its own risks in terms of bias. More generally, recruitment to trials often has ebb and flows during the life cycle of a trial for various reasons, and this could have led to some bias being included in the comparison.

Participants in the IONTI-2 study were given an 'opt-out' option when receiving the £30 voucher. This was taken up by a small proportion [5% (24/481)] of participants, but the true 'opt-out' level may include some who did not respond.

Summary

The IONTI studies did not find any evidence in favour of the use of incentives to increase the response rate, and there was some suggestion of a negative impact. There are a number of contextual aspects that may explain this unexpected finding. Care is needed when introducing a new intervention into an ongoing study. Future evaluations of incentives are needed to explore the impact of contextual issues that may moderate their impact.

Chapter 9 Patient preference

Introduction

Patients' preference regarding treatment is well acknowledged to have a potential impact on the generalisability of randomised trials.⁶¹ This can occur if an unrepresentative group of individuals (when compared with the patient population, who would potentially receive the treatments under evaluation) participate in the study. Perhaps less well recognised is the potential for patients' treatment to have an impact on the study results.^{62,63} Participants within trials who receive their preferred treatment may have different outcomes from those who do not, as they may be more motivated to continue participating in the study (e.g. complying with the treatment) or simply perceive their outcome as being better as a result of receiving their preference. Those who do not receive their preferred treatment may experience resentful demoralisation and be more likely to drop out of the study.⁶²

Various modifications to study design have been proposed to allow exploration of the impact of patients' treatment preference. These include preference study design (a form of comprehensive cohort in which those who do not consent to take part in a RCT receive their preferred treatment) and the fully randomised patient preference design.^{62,64,65} Various advantages and disadvantages of these approaches have been considered elsewhere.^{62,65}

Previous work has suggested, as noted in *Chapter 1*, that TH and SH procedures have different outcome profiles; one (SH) potentially leads to less pain and better quality of life in the short term, and the other (TH) potentially leads to less recurrence and need for further intervention. The eTHoS study aimed to evaluate the comparative effectiveness of these procedures over 24 months and, as shown in *Chapters 5* and *6*, this was confirmed by the study. Given this, there was reason to anticipate that patients' preferences had the potential to have an impact on the study findings as well as on recruitment.⁶² We were unaware of any assessment of the impact of patients' preference for the treatment of haemorrhoids. To address this, we adopted a fully randomised patient preference design in which participants' preferences were recorded at baseline, prior to randomisation. This enabled an analysis that takes preference into account. In this chapter, we report the findings of the fully randomised patient preference evaluation. Consideration of the impact of preference is briefly made in *Chapter 5*, in which reasons for not participating are recorded. An alternative evaluation of patient preferences was undertaken in the DCE reported in *Chapter 7*.

Methods

Measuring participants' treatment preference

We recorded the preference in an indirect way by including a question about preference in the baseline question. The questionnaire was framed around two hypothetical treatments, A and B. It was stated that treatment A was believed to have better short-term recovery (up to 6 weeks), but over the longer term (up to 5 years) patients may be more likely to have haemorrhoids again and need further surgery. Treatment B was believed to have poorer short-term recovery (up to 6 weeks), but over the longer term (up to 5 years) patients were less likely to have haemorrhoids again and need further surgery. Participants were asked for their choice of treatment on a five-point Likert scale (the options were 'strongly prefer operation A', 'prefer A but not strongly', 'no preference', 'prefer B but not strongly' and 'strongly prefer B'). These scenarios (A and B) were a simplification of the expectation regarding SH and TH at the initiation of the study, given previous evidence.^{2,13} Details of how the baseline questionnaire data were collected and information relating to the study design are provided in *Chapter 3*.

Statistical analysis

Participants' treatment preferences were separated by the two interventions, SH and TH, and important baseline characteristics were summarised according to the preference choice. The primary outcome, EQ-5D-3L, key patient-reported secondary outcomes at 24 months (CIS, HSS and recurrence) and treatment by preference group interactions were included. Compliance with treatment allocation and retention were compared between groups using a logistic regression with interaction effects for the preference groups as above. Continuous variables were summarised with number, mean (SD) or median and IQR, and discrete variables were number and percentages. All analyses were at the 5% two-sided significance level with 95% CIs provided as appropriate and analysed using Stata.

Results

Of the 774 participants randomised (after three post-randomisation exclusions), 766 completed the preference question. A total of 307 (40.1%) had no preference, with more participants strongly preferring operation B [159 (20.8%)] over A [61 (8.0%)] (*Table 59*). Preference groups were balanced between the two randomised interventions.

There was no sign of a difference in outcome between the participants' treatment preference at baseline in terms of overall or disease-specific quality of life (*Table 60*). Those who preferred operation A (strongly or not) were slightly younger, and more men strongly preferred A.

The EQ-5D-3L data according to the participants' preference across all time points are given in *Table 61*. At baseline, the groups differed noticeably in EQ-5D-3L score, although not in a manner consistent with a preference effect. As was observed in the main study analysis (see *Chapter 5*), the scores were lower at 1 week and 3 weeks post surgery. At 3 weeks, preference of operation A (but not strongly) had a higher score than the other preference groups, and at 12 months post randomisation, the score was lower in the strongly preferring operation A group. Results of the analyses that assessed the impact of the preference on the randomised group comparison of the primary outcome are given in *Table 62*.

The EQ-5D-3L preference analyses at 6 weeks and 12 months did not show any clear statistical evidence of an interaction between treatment and preference (at most one of the interaction effects was statistically significant at the 5% level). Although the observed difference within subgroups did differ somewhat, at 12 and 24 months they all tended towards favouring TH. The pattern was not consistent in terms of a preference effect.

TABLE 59 Participants' treatment preference

Treatment preference	Trial arm, n (%)		Total, n (%)
	SH	TH	
No preference	161 (41.5)	146 (37.8)	307 (40.1)
Prefer operation A but do not feel very strongly	35 (9.0)	24 (6.2)	59 (7.7)
Strongly prefer operation A	23 (5.9)	38 (9.8)	61 (8.0)
Prefer operation B but do not feel very strongly	95 (24.5)	85 (22.0)	180 (23.5)
Strongly prefer operation B	68 (17.5)	91 (23.6)	159 (20.8)
Total	382	384	766 (100.0) ^a

^a Eight randomised participants did not complete the treatment preference question.

TABLE 60 Baseline characteristics by participants' treatment preference

Characteristic	Treatment preference				
	No preference (N = 307)	Prefer operation A but do not feel very strongly (N = 59)	Strongly prefer operation A (N = 61)	Prefer operation B but do not feel very strongly (N = 180)	Strongly prefer operation B (N = 159)
Age (years), <i>n</i> , median (IQR)	307, 51 (41–62)	59, 46 (36–55)	61, 47 (40–56)	180, 49 (40–60)	159, 49 (40–59)
Sex (male), <i>n</i> (%)	159 (51.8)	28 (47.5)	41 (67.2)	84 (46.7)	82 (51.6)
EQ-5D-3L, <i>n</i> , mean score (SD)	307, 0.754 (0.255)	59, 0.797 (0.202)	61, 0.756 (0.287)	180, 0.801 (0.221)	159, 0.727 (0.295)
SF-36, <i>n</i> , mean score (SD)					
Physical component summary	299, 48.5 (9.7)	59, 51.6 (6.2)	59, 50.2 (7.7)	176, 49.3 (8.8)	158, 46.8 (10.7)
Mental component summary	299, 49.4 (11.0)	59, 48.7 (10.7)	59, 49.1 (10.4)	176, 50.1 (10.6)	158, 48.0 (13.2)
CIS	297, 4.3 (3.9)	59, 4.3 (3.7)	60, 4.3 (4.0)	175, 3.8 (3.8)	155, 4.2 (4.4)
HSS	289, 12.7 (4.1)	58, 12.7 (3.6)	58, 12.4 (3.4)	175, 12.5 (3.5)	154, 12.7 (4.2)

TABLE 61 EuroQol-5 Dimensions, three-level version by treatment preference

Time point	Treatment preference, <i>n</i> , mean score (SD)				
	No preference (N = 307)	Prefer operation A but do not feel very strongly (N = 59)	Strongly prefer operation A (N = 61)	Prefer operation B but do not feel very strongly (N = 180)	Strongly prefer operation B (N = 159)
Baseline	307, 0.754 (0.255)	59, 0.797 (0.202)	61, 0.756 (0.287)	180, 0.801 (0.221)	159, 0.727 (0.295)
1 week	233, 0.529 (0.340)	49, 0.520 (0.315)	41, 0.588 (0.293)	141, 0.546 (0.323)	120, 0.478 (0.352)
3 weeks	229, 0.765 (0.281)	47, 0.814 (0.224)	37, 0.723 (0.258)	129, 0.794 (0.218)	115, 0.784 (0.182)
6 weeks	243, 0.828 (0.265)	46, 0.890 (0.140)	44, 0.849 (0.170)	147, 0.877 (0.184)	123, 0.839 (0.223)
12 months	227, 0.828 (0.262)	45, 0.866 (0.184)	34, 0.794 (0.250)	146, 0.877 (0.190)	118, 0.858 (0.246)
24 months	225, 0.851 (0.228)	40, 0.846 (0.235)	35, 0.835 (0.214)	134, 0.876 (0.172)	115, 0.836 (0.257)

The randomised treatment by participants' preference analyses for HSS and CIS are given in *Table 63*. The CIS and HSS preference analyses at 24 months did not show any clear statistical evidence of an interaction between treatment and preference (none and one of the interaction effects, respectively, were statistically significant at the 5% level). All within-subgroup effects tended in the direction of favouring TH.

TABLE 62 The EQ-5D-3L AUC by treatment preference

Time point and treatment preference	n, mean AUC (SD)	Interaction effect		Within-preference-subgroup treatment effect	
		MD (95% CI)	p-value	MD (95% CI)	p-value
6 weeks					
No preference	261, 0.205 (0.137)	–	–	0.043 (–0.001 to 0.087)	0.057
Prefer operation A but do not feel very strongly	55, 0.192 (0.149)	–0.083 (–0.188 to 0.023)	0.121	–0.040 (–0.118 to 0.039)	0.309
Strongly prefer operation A	48, 0.212 (0.134)	–0.026 (–0.096 to 0.044)	0.451	0.017 (–0.060 to 0.094)	0.655
Prefer operation B but do not feel very strongly	155, 0.216 (0.155)	–0.005 (–0.079 to 0.068)	0.880	0.038 (–0.004 to 0.079)	0.072
Strongly prefer operation B	135, 0.203 (0.162)	–0.052 (–0.118 to 0.014)	0.115	–0.009 (–0.058 to 0.039)	0.695
12 months					
No preference	216, 0.800 (0.236)	–	–	0.048 (–0.010 to 0.105)	0.099
Prefer operation A but do not feel very strongly	44, 0.888 (0.258)	–0.123 (–0.322 to 0.076)	0.228	–0.076 (–0.264 to 0.112)	0.415
Strongly prefer operation A	30, 0.845 (0.164)	–0.127 (–0.227 to –0.028)	0.014	–0.080 (–0.163 to 0.003)	0.057
Prefer operation B but do not feel very strongly	136, 0.849 (0.187)	–0.057 (–0.124 to 0.009)	0.088	–0.010 (–0.059 to 0.039)	0.681
Strongly prefer operation B	113, 0.822 (0.221)	–0.120 (–0.226 to –0.014)	0.027	–0.072 (–0.147 to 0.003)	0.058
24 months					
No preference	230, 1.565 (0.471)	–	–	0.025 (–0.081 to 0.131)	0.629
Prefer operation A but do not feel very strongly	47, 1.575 (0.504)	–0.174 (–0.436 to 0.089)	0.187	–0.148 (–0.374 to 0.077)	0.188
Strongly prefer operation A	34, 1.582 (0.416)	–0.165 (–0.454 to 0.124)	0.252	–0.140 (–0.418 to 0.138)	0.312
Prefer operation B but do not feel very strongly	137, 1.633 (0.410)	–0.117 (–0.228 to –0.005)	0.042	–0.091 (–0.180 to –0.002)	0.045
Strongly prefer operation B	117, 1.590 (0.474)	–0.187 (–0.372 to –0.002)	0.048	–0.162 (–0.334 to 0.010)	0.064

Table 64 shows the patient-reported recurrence preference analyses at 24 months, which did not show any clear statistical evidence of an interaction between treatment and preference (none of the respective interaction effects was statistically significant at the 5% level). All within-subgroup effects tended in the direction of favouring TH.

The compliance with treatment preference analyses (Table 65) did not show any clear statistical evidence of an interaction between treatment and preference (none of the respective interaction effects were statistically significant at the 5% level). All within-subgroup effects tended in the direction of favouring TH. Table 66 shows the association between compliance and retention and participants' treatment preferences.

TABLE 63 The CIS and HSS by treatment preference at 24 months post randomisation

Outcome and treatment preference	n, mean score (SD)	Interaction effect		Within-preference-subgroup treatment effect	
		MD (95% CI)	p-value	MD (95% CI)	p-value
CIS					
No preference	196, 3.67 (3.82)	–	–	0.452 (0.355 to 0.549)	< 0.001
Prefer operation A but not feel very strongly	32, 3.25 (2.98)	–0.14 (–2.02 to 1.73)	0.875	0.356 (–1.042 to 1.754)	0.606
Strongly prefer operation A	28, 4.11 (2.95)	–0.43 (–2.04 to 1.18)	0.589	0.072 (–1.318 to 1.462)	0.916
Prefer operation B but not feel very strongly	121, 2.98 (3.25)	0.26 (–1.03 to 1.54)	0.686	0.758 (–0.066 to 1.582)	0.070
Strongly prefer operation B	103, 3.44 (3.95)	1.27 (–0.09 to 2.62)	0.066	1.768 (0.458 to 3.078)	0.010
HSS					
No preference	198, 5.46 (4.64)	–	–	0.52 (–0.591 to 1.628)	0.347
Prefer operation A but not feel very strongly	33, 6.12 (4.86)	0.47 (–1.66 to 2.60)	0.654	0.99 (–0.726 to 2.704)	0.247
Strongly prefer operation A	30, 6.90 (4.72)	2.92 (0.20 to 5.65)	0.036	3.44 (0.932 to 5.951)	0.009
Prefer operation B but not feel very strongly	119, 5.77 (4.99)	1.99 (–0.02 to 4.01)	0.052	2.51 (1.141 to 3.886)	0.001
Strongly prefer operation B	105, 5.23 (4.81)	1.57 (–0.29 to 3.43)	0.094	2.09 (0.373 to 3.813)	0.019

TABLE 64 Participant-reported recurrence at 24 months by preference effect

Treatment preference	n (%)	Interaction effect		Within-preference-subgroup treatment effect	
		OR (95% CI)	p-value	OR (95% CI)	p-value
No preference	89 (36.6)	–	–	2.77 (1.66 to 4.63)	< 0.001
Prefer operation A but not feel very strongly	14 (28.6)	0.78 (0.21 to 2.82)	0.700	2.15 (0.64 to 7.24)	0.217
Strongly prefer operation A	11 (27.5)	0.55 (0.18 to 1.64)	0.283	1.52 (0.44 to 5.20)	0.509
Prefer operation B but not feel very strongly	57 (37.7)	0.69 (0.36 to 1.34)	0.278	1.92 (1.01 to 3.64)	0.046
Strongly prefer operation B	36 (28.3)	0.78 (0.31 to 1.95)	0.594	2.16 (0.88 to 5.26)	0.091

TABLE 65 Compliance with treatment allocation

Treatment preference	Compliance within subgroup, <i>n</i> (%)		Interaction effect		Within-preference subgroup treatment effect	
	Yes	No	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
No preference	51 (16.6)	256 (83.4)	–	–	–	–
Prefer operation A but not feel very strongly	11 (18.6)	48 (81.4)	2.392 (0.591 to 9.678)	0.222	1.264 (0.437 to 3.659)	0.665
Strongly prefer operation A	18 (29.5)	43 (70.5)	3.631 (0.785 to 16.805)	0.099	1.920 (0.559 to 6.590)	0.300
Prefer operation B but not feel very strongly	35 (19.4)	145 (80.6)	1.015 (0.334 to 3.085)	0.978	0.537 (0.266 to 1.083)	0.082
Strongly prefer operation B	32 (20.1)	127 (79.9)	1.123 (0.266 to 4.739)	0.874	1.594 (0.275 to 1.283)	0.185

TABLE 66 Retention to whole questionnaire at 24 months

Treatment preference	Response to questionnaire, <i>n</i> (%)		Interaction effect		Within-preference subgroup treatment effect	
	Yes	No	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
No preference	80 (26.1)	227 (73.9)	–	–	1.14 (0.70 to 1.84)	0.597
Prefer operation A but not feel very strongly	19 (32.2)	40 (67.8)	1.004 (0.341 to 2.958)	0.994	1.14 (0.36 to 3.67)	0.822
Strongly prefer operation A	25 (41.0)	36 (59.0)	0.925 (0.378 to 2.264)	0.865	1.05 (0.46 to 2.40)	0.901
Prefer operation B but not feel very strongly	43 (23.9)	137 (76.1)	0.860 (0.390 to 1.900)	0.710	0.98 (0.55 to 1.73)	0.943
Strongly prefer operation B	43 (27.0)	116 (73.0)	1.488 (0.931 to 2.378)	0.097	1.69 (1.08 to 2.65)	0.021

There was some suggestion of a preference effect (for the ‘strongly prefer B’ group), which might have lead to differential retention.

Discussion

Patient preference was collected in the eTHoS study, prior to randomisation, by asking participants to give their preference for a hypothetical scenario that reflected general belief at the time of the study’s initiation. The majority of participants in the eTHoS study expressed a preference, with more participants favouring longer-term over short-term outcomes. It is worth noting that among all patients who would receive SH or TH, this proportion could well be higher, as some with stronger preferences are likely to not have consented to participate in the study.

Overall, there was no clear sign of a preference effect for any of the outcomes. This finding held for all of the outcomes (EQ-5D-3L, CIS, HSS, recurrence compliance and retention). There was also no sign of a difference at baseline according to preference group. Similar to other work, we have found that the overall RCT results were not modified by treatment preference.⁶⁶ There was some suggestion of an effect on

retention for strong preference in favour of those who favour long-term reduced recurrence over short-term recovery.

Several trials have been undertaken using this approach to assess the effect of patients' preference on outcome,^{63,67–69} with the proportion expressing a preference varying substantially. Findings regarding whether or not the existence of preferences has affected the treatment effect have been mixed.^{62,63}

Our study is one of the largest to look at within-trial preferences and to assess the possible impact on the treatment effect.⁶³ We are aware of only one previous fully randomised surgery preference study, which was reported for incontinence surgery.⁷⁰ None looked at preference for treatment of haemorrhoids. It may be the condition that explains the lack of preference or that the treatments were of a similar (surgical) nature, though they did differ in expected and realised outcome. The DCE reported in *Chapter 7* explored preferences in a more subtle way and showed a specific preference for particular attributes (lower recurrence and complications). Differences in the included participants may explain this difference in findings, or that while there were some preferences for the nature of treatment outcome, this did not affect the treatment comparison of SH and TH.

There were a number of limitations to this work. First, the preference of participants was measured indirectly and fairly crudely. The terminology we used may not have produced a fully balanced response and contributed to some degree to the favouring of B over A, aside from solely the participants' general preference for longer-term resolution even at the cost of poor short-term outcome. The response would link to the timings we used, which reflected the views on the relative impact of the operation and the anticipated last timing of outcome assessed (6 weeks and 2 years). We asked participants in the eTHoS study directly about any preference, whereas in other studies this was assessed by the health professional.⁷¹

Summary

No clear evidence of a treatment preference effect was observed. These analyses further support the generalisability of the main study results and that TH has a better outcome over 24 months than SH. Further work exploring which types of treatment choices are more likely to have stronger associated patient preferences would be beneficial.

Chapter 10 Discussion

Summary of findings

The eTHoS study is one of the largest studies conducted in the field of haemorrhoidal disease worldwide. The findings from the study, along with those from HubBLLe and LingaLongo,^{16,72} have added greatly to our understanding of the management of haemorrhoids. This study showed better overall generic quality of life over the 24-month follow-up period for TH over SH. Drawing on previous work concerning clinically important differences in the EQ-5D-3L, the magnitude of difference in favour of TH was found to be clinically important. The minimum important difference for the EQ-5D-3L has been estimated to be around 0.07, based on an anchor method applied to a range of patient populations.^{73,74} The participants who were randomised to receive TH also reported fewer haemorrhoid symptoms and less incidence of further surgery in the 24-month follow-up period. Incontinence symptoms and tenesmus also occurred less frequently in this arm. In the immediate postoperative period, those who were randomised to receive SH reported less pain, but this difference disappeared by 6 weeks. Short-term post-surgery quality of life (measured by the EQ-5D-3L) scores also favoured SH, reflecting the lower rates of pain and analgesic consumption. At 12 months, the EQ-5D-3L AUC quality-of-life scores were similar; however, the physical and mental health domains of the SF-36 favoured TH (see *Table 17*). By the end of the 24-month follow-up period, the primary outcome favoured TH. This, along with lower residual symptoms, re-interventions and costs, indicates that TH may be the surgical treatment of choice for grades II–IV haemorrhoids. Overall, this suggests that TH is the better treatment option in terms of clinical effectiveness.

The operating time, length of stay and return to normal activity by 6 weeks were the same in both arms of the study. This differs from the previously published economic studies that suggested that a shorter operating time, and associated length of hospital stay after SH, offset the cost of a stapler.² This fact, taken alone, draws into question the continued use of the technique, as it implies higher costs for a similar surgical outcome. The ongoing use of SH within publicly funded health services is also challenged by the other findings from this study that demonstrate a higher recurrence rate, more tenesmus, higher cost and otherwise equivocal incontinence scores and complications. Even the reduced pain after SH was equivalent by 6 weeks postoperatively.

Strengths and limitations

In the eTHoS study, the clinical recurrence of haemorrhoids and severity of symptoms were measured using the HSS, a patient-reported, dichotomous outcome measure, which was supplemented with recurrence data from both national registry databases (HES, PEDW and ISD) and patients' self-reported further interventions. HSS is not a validated tool; however, it was adopted in the HubBLLe study,¹⁶ and at the inception of the eTHoS study it was arguably the best assessment tool available. An initial follow-up period of 24 months for the evaluation of outcomes was used, given the expectation of a trade-off between short- and longer-term outcomes as transpired. We expected the majority of recurrences of haemorrhoids to happen in the first 24 months of the study; however, there were very few data available concerning the long-term success rates of haemorrhoid surgery. Extending the follow-up period to 60 months could be advantageous, although it seems unlikely that the direction of effect would change. In addition, after 24 months it would be important to distinguish between those symptoms caused by inadequate initial treatment and the occurrence of new disease.²³

Incontinence and tenesmus are significant symptoms for patients after haemorrhoid surgery. The anal sphincter complex comprises two concentric muscles, the internal and external anal sphincters. Anal cushions (the abnormal swelling of which form the basis of haemorrhoids) in the upper part of the canal

contribute to continence by acting as ‘washers’ helping to form a seal. Prolapsed haemorrhoids, therefore, interfere with continence by disrupting the sealing mechanism of the sphincters and cushions working in concert. TH involves removing tissue close to the internal sphincter. Damage and subsequent impairment of continence is widely reported after TH.⁷⁴ The optimal technique for SH involves the accurate placement of the staple line 3–4 cm from the anal verge and above the dentate line in the columnar mucosa of the anal canal. Staple lines lower than this may encroach on the squamous mucosa of the anal canal (which has the sensory inputs of normal skin), contributing to relatively more postoperative pain and a greater chance of injuring the internal sphincter.⁷⁵ In the immediate postoperative period, continence was relatively impaired when compared with the baseline, reasonably attributable to subsequent pain and healing in this sensitive area (see *Table 17*). However, continence scores were significantly better in the TH arm up to 24 months after randomisation. High-quality surgery and the avoidance of sphincter injury in both arms, as well as reducing the volume of haemorrhoid tissue, would explain the slight improvement in continence scores over the course of the study.

Meaning of the study

The economic analysis convincingly demonstrated that TH dominates SH, as it costs £337 less than SH and is 0.07 QALYs more clinically effective than SH. SH has a < 1% probability of being considered cost-effective at the £30,000 threshold. Taken together with the HubBLE study’s health-care cost analysis, this suggests that neither of the newer surgical techniques are cost-effective. The results of the economic analysis differ from those published in Burch *et al.*², in which it was reported that TH and SH had similar costs and QALYs, but that the costs of the staple gun were offset by savings in hospital stay. In our study, the inpatient stay was similar in both arms, so there were no cost-savings in inpatient stay, and our QALY results, based on a 24-month follow-up, indicate that SH had fewer QALYs than TH (see *Tables 34–36*). There is a paucity of robust economic data available on haemorrhoid surgery; however, if the results of the eTHoS and HubBLE studies are adopted into practice, substantial annual cost-savings in publicly funded health services could be achieved. Given the current financial status of the NHS, commissioners of health care may consider being more prescriptive about procedures being offered for haemorrhoids.

Study design and conduct

Within this study we ran two substudies (SWATs) examining the effectiveness of incentives in maximising questionnaire returns. The SWATs were developed and conducted using vouchers with different monetary values, £5 and £30. The first SWAT, the IONTI study, was stopped early as the study team feared that it was having a negative impact on retention. The monetary value was increased to £30 (IONTI-2 study), but, again, this had little impact on response rates. The use of financial incentives is an under-researched but important area in the recruitment and continued participation of patients within trials. Based on the IONTI studies, we are uncertain of whether or not the financial incentives met a high enough threshold value to influence participant behaviour, if the participants’ motives to take part in research trials were more altruistic, if the negative result of the IONTI study was a chance finding, if there were study-specific factors or if a combination of these explain the unanticipated findings.

Participants’ treatment preferences have been suggested to potentially have a substantial impact on the outcome. As part of the study we explored this in two ways. The design of the eTHoS study included a DCE. We wanted to use this methodology to explore what attributes about an operation may influence patient choice. The DCE data were collected iteratively through a user group, a public group (on the internet) and then through participants who had completed their 24-month questionnaires. The attributes and levels were developed robustly. Overall, respondents in both groups had a general preference to have treatment over no treatment, but did not distinguish between the three treatment options. However, they also had preferences for the attributes identified, with decreases in all four treatment attributes, as expected, reducing the benefit of treatment. The magnitude of coefficients indicated that the most

important marginal changes were chance of recurrence followed by chance of complications. A further novel addition to the eTHoS study was the patient preference study embedded within it. We believe this to be the first prospectively conducted preference study of patients with haemorrhoids within a RCT. Participants were asked, prior to randomisation, if they had a preference for one of the treatment modalities. Although the choices of treatments were described abstractly as surgeries 'A' and 'B', participants were more likely to favour an operation that gave them longer-term disease control but poorer short-term outcomes. Pre-randomisation preferences had no clear influence on retention or outcomes within this study.

Taken together, the findings from these two approaches to explore preferences further support the strength of the overall findings of the eTHoS study.

Results in context

The interventions compared in the eTHoS study reflected clinical practice in the UK NHS at the time of its design. During the recruitment period a new intervention, HAL, was being adopted. The HubBLE trial recently showed no benefit to HAL over RBL.¹⁶ The HUBBLE and eTHoS studies suggest a pattern of failure of new, and purportedly better, interventions to achieve sufficient clinical outcome at an appropriate cost. They provide a cautious warning about the widespread adoption of relatively expensive and unproven new procedures. The IDEAL framework^{76–78} provides a potential pathway from idea to robust evaluation; however, to date, while perhaps improving, surgical evaluation is still often too late and lacking in rigour.

The introduction of new surgical treatments for haemorrhoids has been accompanied by the greater incidence of reporting of adverse events. There have been some published postoperative complications, after surgery for a benign condition, which have been severe, particularly with regard to pelvic sepsis, rectal perforation and rectovaginal fistula formation.⁷⁹ There were no reports of these complications within this study, which may reflect safe surgical practice within study centres, or that complications occur more frequently within the earlier stages of surgical learning curves. SAEs were equally distributed through both arms of the eTHoS study. All the events were expected and largely consisted of pain, bleeding, constipation and urinary retention.

A number of decisions were made reflecting the pragmatic nature of the study's conception and design and its aim to reflect routine care. First, the study was unblinded; there was no attempt to blind either the participants (who were generally the outcome assessors) or the surgeon to the intervention. Also, the presence or absence of perianal wounds would have rendered blinding impossible, even in the short term. No prescriptive entry criteria were set for hospital inclusion; we are therefore confident that the results are generalisable across health services. A 24-month follow-up period was used to capture symptom recurrence and further interventions, giving a median follow-up of 731 days, which is an additional strength of this study.

A pragmatic approach to surgeon's credentials was adopted. At the inception of the study, both techniques were established in common surgical practice and surgeons had to have undergone appropriate recognised training for both procedures. Ideally, this would also have included attendance at a 'masterclass'. The effect of surgical experience on outcomes can partially be mitigated by the high level of consultant involvement in performing the surgery (71.5% in the SH arm and 62.0% in the TH arm) and the low incidence of adverse events.

There were perhaps four key potential sources of bias. First, the study was, as noted above, unblinded. However, given the lack of the evidence to support a patient preference effect, this seems unlikely to have given a biased effect. Second, final recruitment to the eTHoS study was just short (97%) of the target number; and third, there were a substantial number of missing data at the 24-month follow-up despite multiple strategies to mitigate this (IONTI and IONTI-2 studies). This perhaps reflected the population (working age), the nature of the condition (chronic and considered by some to be a sensitive subject) and

the nature of the follow-up. Nevertheless, the study still had sufficient statistical precision to detect a clinically relevant difference between treatment groups. The presence of a substantial number of missing data could have led to bias being introduced into the comparison. Various secondary analyses explored plausible imputation and missing data assumptions regarding quality of life, and there was a consistent pattern of benefit in favour of TH over 24 months. Fourth, there was also a noticeable amount of non-compliance with allocation (some participants not receiving surgery, and some receiving a different operation), reflecting perhaps a mixture of clinical reality and also some surgeon and patient preferences regarding treatment. Such non-compliance tends to dilute a genuine effect. Despite this, the primary analysis still supported a difference in favour of TH, and the per-protocol analysis of only those who complied with allocation was consistent in the findings. More generally, it is worth noting that the delivery of the interventions reflected routine clinical practice across a range of UK centres in terms of the surgeons participating (their experience) and how the interventions were delivered (specific technique and centre practices). Taken together, we believe the findings are robust and generalisable.

Recommendations

The findings in this study can be compared with a recent network meta-analysis that included 98 trials of procedures for grade III and IV haemorrhoids in the analysis.²³ The authors suggested that TH was associated with fewer haemorrhoid recurrences, and that SH was associated with less postoperative pain and with a higher rate of recurrence. However, the eTHoS study findings refute the data on higher complications rates, return to normal activity, length of operation and length of stay in TH. Taken together, the HubBLE¹⁶ and eTHoS trials also answer the authors' call for further high-quality RCTs incorporating economic cost comparisons. Our recommendation for future work would be to update a network meta-analysis incorporating these two large trials, with the addition of the LingaLongo study, which would add further value to the existing literature.

Conclusions

In conclusion, excisional surgery (TH) was both more clinically effective and less costly than SH. It was more painful in the short term, but this level of pain can be adequately managed at home. Return to normal activity rates were equal. In addition to superior quality-of-life scores, haemorrhoid symptoms scores, continence and tenesmus rates and the need for further surgery were all lower in TH. TH is, therefore, a superior surgical treatment for the management of grades II–IV haemorrhoids when compared with SH in terms of clinical effectiveness and cost-effectiveness.

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The eTHoS study group comprises Angus JM Watson, Kathleen MacLeod, Malcolm Loudon, David Jayne, Ramesh Rajagopal, Finlay Curran, Steven Brown, Jonathan Cook, John Norrie, Brian Buckley, Mary Kilonzo, Jessica Wood, Alison McDonald and Mark Forrest (who replaced Gladys McPherson on 1 July 2015).

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Contributions of authors

Professor Angus JM Watson (Consultant Colorectal Surgeon) was the chief investigator of the study; he had complete involvement and oversight of the study design, execution and data collection, and was responsible for the final report.

Professor Jonathan Cook (Senior Statistician/Triallist) contributed his methodological expertise to the design of the study, recruitment and interpretation of the study findings, and to the writing and delivery of the final report.

Miss Jemma Hudson (Statistician) contributed to the statistical analysis of the study and writing of the results and discussion chapters.

Ms Mary Kilonzo (Research Fellow, Health Economics and co-investigator) contributed to the analysis of the health economics component of the study and also to the writing of the health economics chapters.

Mrs Jessica Wood (Trial Manager) was responsible for the day-to-day management and delivery of the study, and the writing and delivery of the final report.

Dr Hanne Bruhn (Research Fellow) contributed to the delivery of the study and the writing and delivery of the final report.

Mr Steven Brown (Consultant Colorectal Surgeon) contributed to the design and delivery of the study, and to the writing of the final report.

Dr Brian Buckley (Patient representative) contributed to the design and delivery of the study, and to the writing of the final report.

Mr Finlay Curran (Consultant Colorectal Surgeon) contributed to the design of the study, delivery of the study and to the writing of the final report.

Mr David Jayne (Consultant Colorectal Surgeon) contributed to the design and delivery of the study, and to the writing of the final report.

Mr Malcolm Loudon (Consultant Colorectal Surgeon) contributed to the design and delivery of the study, and to the writing of the final report.

Mr Ramesh Rajagopal (Consultant Colorectal Surgeon) contributed to the design and delivery of the study, and to the writing of the final report.

Mrs Alison McDonald (Senior Trial Manager) contributed to the delivery of the study and to the writing of the final report.

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Data sharing statement

All available data can be obtained by contacting the corresponding author.

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Appendix 1 The eTHoS study participant questionnaire

BASELINE QUESTIONNAIRE

Study No

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PARTICIPANT QUESTIONNAIRE

BASELINE

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 3.1, June 2012

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 cross (x) 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 questionnaire filled in

D	D	M	M	Y	Y	Y	Y
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SECTION A: DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today. (For nurse use only: numbers 1-3 in brackets, relate to telephone randomisation procedure).

- | | | |
|--|--|------------------------------|
| A1. Mobility | I have no problems in walking about | ☐ (1) |
| | I have some problems in walking about | ☐ (2) |
| | I am confined to bed | ☐ (3) |
| A2. Self-care | I have no problems with self-care | ☐ (1) |
| | I have some problems washing or dressing myself | ☐ (2) |
| | I am unable to wash or dress myself | ☐ (3) |
| A3. Usual Activities
(e.g. work, study, housework, family or leisure activities) | I have no problems with performing my usual activities | ☐ (1) |
| | I have some problems with performing my usual activities | ☐ (2) |
| | I am unable to perform my usual activities | ☐ (3) |
| A4. Pain/Discomfort | I have no pain or discomfort | ☐ (1) |
| | I have moderate pain or discomfort | ☐ (2) |
| | I have extreme pain or discomfort | ☐ (3) |
| A5. Anxiety/Depression | I am not anxious or depressed | ☐ (1) |
| | I am moderately anxious or depressed | ☐ (2) |
| | I am extremely anxious or depressed | ☐ (3) |

[Section B: Your General Health (SF-36©) has been removed due to copyright]

SECTION C : ASSESSMENT OF FAECAL (STOOL) INCONTINENCE

This set of questions asks about faecal (stool) incontinence. Can you please mark with an X in the appropriate box if you have experienced any of the following in the past 4 weeks:

	Always	Often	Sometimes	Rarely	Never
C1. Incontinence of solid stool	☐	☐	☐	☐	☐
C2. Incontinence of liquid stool	☐	☐	☐	☐	☐
C3. Incontinence of gas	☐	☐	☐	☐	☐
C4. Need to wear a pad or plug	☐	☐	☐	☐	☐
C5. Altered your lifestyle	☐	☐	☐	☐	☐

“always” = one or more times daily, “often” = more than once a week but less than once daily; “sometimes” = more than once a month but less than once a week; “rarely” = less than once a month.

SECTION D : HAEMORRHOIDS SYMPTOM SCORE

	Less than 1 year	Up to 1 year	Up to 5 years	More than 5 years
D1. How long have you had haemorrhoid symptoms?	☐	☐	☐	☐

This set of questions asks you about any symptoms related to haemorrhoids that you have had in the past 4 weeks. Please mark an X in the appropriate box.

	None	Spotting	Staining underwear	Dripping into pan	Without stool
D2. Any bleeding from your back passage?	☐	☐	☐	☐	☐

	None	Only with stool	Constant throbbing
D3. Any pain in your back passage?	☐	☐	☐

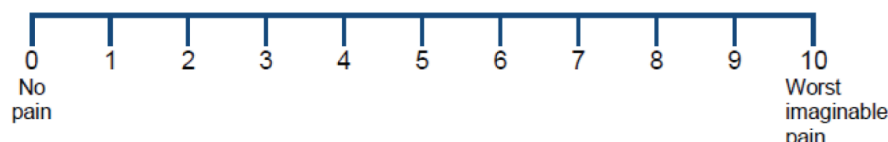
D4. Do you have any of the following other symptoms:

	Always	Often	Sometimes	Rarely	Never
a) Prolapse (a sensation of something coming down out of your back passage)	☐	☐	☐	☐	☐
b) Itching	☐	☐	☐	☐	☐
c) Mucous discharge	☐	☐	☐	☐	☐
d) Faecal urgency (unable to defer defecation for 15 mins)	☐	☐	☐	☐	☐
e) Faecal frequency (more often than before you had haemorrhoids)	☐	☐	☐	☐	☐

- | | Always | Often | Sometimes | Rarely | Never |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| D5. Have you suffered with tenesmus (a constant sensation in your back passage, which gives you an urge to move your bowel)? | ☐ | ☐ | ☐ | ☐ | ☐ |

SECTION E: YOUR LEVEL OF PAIN

- E1. 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.



- E2. During the last 7 days have you been taking any pain relief medication? Yes ☐ No ☐

If Yes, how many days, out of the last 7, have you taken any pain relief medication?

- ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

SECTION F: YOUR PREFERENCE

Imagine there are only two treatments (operations A and B) for your haemorrhoids.

One of the two operations (A) is believed to have better short-term (in the first 6 weeks after the operation) recovery but, over the longer term (up to five years), patients who have this type of surgery may be more likely to have haemorrhoids again and need further surgery. The other operation (B) is believed to have poorer short-term (first 6 weeks) recovery but the chances of having haemorrhoids again and needing further surgery in the longer term (up to five years) is less likely. We are interested in whether you have any preference or not between these two operations.

If you were to be able to choose between the two operations, would you:

- | | |
|---|--------------------------|
| Strongly prefer operation A | ☐ |
| Prefer operation A but not feel very strongly | ☐ |
| Have no preference at all | ☐ |
| Prefer operation B but not feel very strongly | ☐ |
| Strongly prefer operation B | ☐ |

Thank you very much for being part of the eTHoS 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.

Once you have completed the questionnaire please give it to the research nurse, who you will already have met and spoken with.

If you would like any further information or have any queries about the study, please contact:

**eTHoS Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD**

Tel: [REDACTED]

E-mail: [REDACTED]
[REDACTED]

Study No

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PARTICIPANT QUESTIONNAIRE

1 WEEK

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 1.1, January 2012

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

Some of the sections ask you to indicate your answers to the questions by placing a cross (X) in the appropriate box, and other sections ask you to circle your answer. 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 questionnaire filled in

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Your date of birth

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

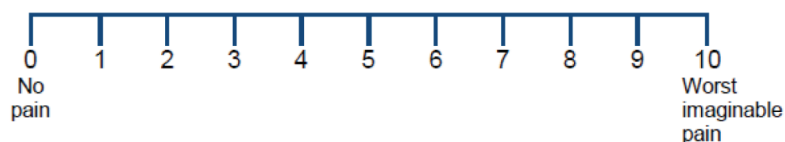
SECTION A: DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

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

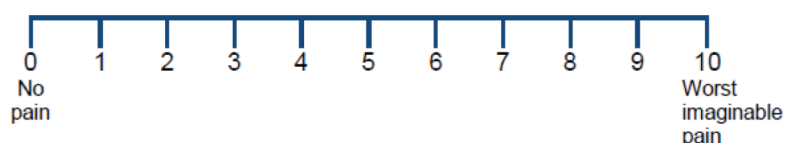
A1. Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐
A3. Usual Activities (e.g. work, study, housework, family or leisure activities)	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
A4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/ Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

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.**



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.**



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

If Yes, 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 eTHoS study and
your time and patience in filling in this questionnaire.

**Please send the questionnaire back to us in Aberdeen
in the prepaid envelope provided.**

**If you would like any further information or have any queries about the study,
please contact:**

**eTHoS Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD
Tel: [REDACTED]
E-mail: [REDACTED]
[REDACTED]**

ISRCTN80061723

Version 1.1, January 2012

Study No

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PARTICIPANT QUESTIONNAIRE

3 WEEKS

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 1, February 2010

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

Some of the sections ask you to indicate your answers to the questions by placing a cross (X) in the appropriate box, and other sections ask you to circle your answer. 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 questionnaire filled in

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

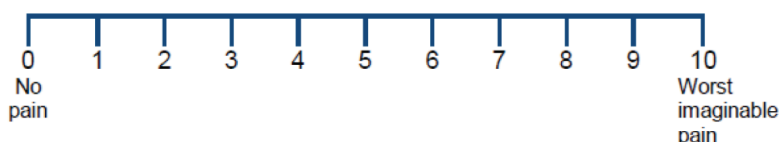
SECTION A: DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

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 some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some 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 with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
A4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/ Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

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.



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

If Yes, 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 eTHoS study and 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.

Please send the questionnaire back to us in Aberdeen in the prepaid envelope provided.

If you would like any further information or have any queries about the study, please contact:

eTHoS Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD

Tel: [REDACTED]

E-mail: [REDACTED]

Study No

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PARTICIPANT QUESTIONNAIRE

6 WEEK

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 2.2, June 2012

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.

Some of the sections ask you to indicate your answers to the questions by placing a cross (x) in the appropriate box, and other sections ask you to circle your answer. 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 questionnaire filled in

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

SECTION A: DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

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 some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some 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 with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
A4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

[Section B: Your General Health (SF-36©) has been removed due to copyright]

SECTION C : ASSESSMENT OF FAECAL (STOOL) INCONTINENCE

This set of questions asks about faecal (stool) incontinence. Can you please mark with an X in the appropriate box if you have experienced any of the following in the past 4 weeks:

	Always	Often	Sometimes	Rarely	Never
C1. Incontinence of solid stool	☐	☐	☐	☐	☐
C2. Incontinence of liquid stool	☐	☐	☐	☐	☐
C3. Incontinence of gas	☐	☐	☐	☐	☐
C4. Need to wear a pad or plug	☐	☐	☐	☐	☐
C5. Altered your lifestyle	☐	☐	☐	☐	☐

“always” = one or more times daily, “often” = more than once a week but less than once daily; “sometimes” = more than once a month but less than once a week; “rarely” = less than once a month.

SECTION D : HAEMORRHOIDS SYMPTOM SCORE

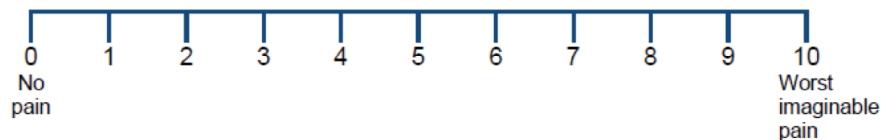
This set of questions asks you about any symptoms related to haemorrhoids that you have had in the past 4 weeks. Please mark an X in the appropriate box.

	None	Spotting	Staining underwear	Dripping into pan	Without stool
D1. Any bleeding from your back passage?	☐	☐	☐	☐	☐
	None	Only with stool	Constant throbbing		
D2. Any pain in your back passage?	☐	☐	☐		
D3. Do you have any of the following other symptoms:					
	Always	Often	Sometimes	Rarely	Never
a) Prolapse (a sensation of something coming down out of your back passage)	☐	☐	☐	☐	☐
b) Itching	☐	☐	☐	☐	☐
c) Mucous discharge	☐	☐	☐	☐	☐
d) Faecal urgency (unable to defer defecation for 15 mins)	☐	☐	☐	☐	☐
e) Faecal frequency (more often than before you had haemorrhoids)	☐	☐	☐	☐	☐

- Always Often Sometimes Rarely Never
- D4.** Have you suffered with tenesmus (a constant sensation in your back passage, which gives you an urge to move your bowel)?
- ☐ ☐ ☐ ☐ ☐

SECTION E: HOW YOU HAVE BEEN SINCE YOUR OPERATION

E1. 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.



- E2.** During the last 7 days have you been taking any pain relief medication? Yes ☐ No ☐

If Yes, how many days, out of the last 7, have you taken any pain relief medication?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

- E3.** Have you returned to your usual activities? Yes ☐ No ☐
(either employment or your normal day to day routine)?

If yes, approximately how many days after you had your haemorrhoid operation were you able to return to your usual activities?
(either employment or your normal day to day routine)

Thank you very much for being part of the eTHoS study and
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.

**Please send the questionnaire back to us in Aberdeen
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Tel: [REDACTED]
E-mail: [REDACTED]
[REDACTED]**

1 YEAR QUESTIONNAIRE

Study No

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PARTICIPANT QUESTIONNAIRE

1 YEAR since you joined

CONFIDENTIAL

Thank you for helping us with our research.
It is now approximately 1 year since you first joined the eTHoS study.
We would be very grateful if you could complete this questionnaire.

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 2.2, August 2012

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 cross (x) 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 questionnaire filled in

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

SECTION A: DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

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 some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some 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 with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
A4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

[Section B: Your General Health (SF-36©) has been removed due to copyright]

SECTION C: ASSESSMENT OF FAECAL (STOOL) INCONTINENCE

This set of questions asks about faecal (stool) incontinence. Can you please mark with an X in the appropriate box if you have experienced any of the following in the past 4 weeks:

	Always	Often	Sometimes	Rarely	Never
C1. Incontinence of solid stool	☐	☐	☐	☐	☐
C2. Incontinence of liquid stool	☐	☐	☐	☐	☐
C3. Incontinence of gas	☐	☐	☐	☐	☐
C4. Need to wear a pad or plug	☐	☐	☐	☐	☐
C5. Altered your lifestyle	☐	☐	☐	☐	☐

“always” = one or more times daily, “often” = more than once a week but less than once daily; “sometimes” = more than once a month but less than once a week; “rarely” = less than once a month.

SECTION D: HAEMORRHOIDS SYMPTOM SCORE

This set of questions asks you about any symptoms related to haemorrhoids that you have had in the past 4 weeks. Please mark an X in the appropriate box.

	None	Spotting	Staining underwear	Dripping into pan	Without stool
D1. Any bleeding from your back passage?	☐	☐	☐	☐	☐
	None	Only with stool	Constant throbbing		
D2. Any pain in your back passage?	☐	☐	☐		
D3. Do you have any of the following other symptoms:					
	Always	Often	Sometimes	Rarely	Never
a) Prolapse (a sensation of something coming down out of your back passage)	☐	☐	☐	☐	☐
b) Itching	☐	☐	☐	☐	☐
c) Mucous discharge	☐	☐	☐	☐	☐
d) Faecal urgency (unable to defer defecation for 15 mins)	☐	☐	☐	☐	☐
e) Faecal frequency (more often than before you had haemorrhoids)	☐	☐	☐	☐	☐

- Always Often Sometimes Rarely Never
- D4.** Have you suffered with tenesmus (a constant sensation in your back passage, which gives you an urge to move your bowel)?
- ☐ ☐ ☐ ☐ ☐

SECTION E: HOW ARE YOU KEEPING

- E1.** Have your haemorrhoids come back at all? Yes ☐ No ☐
- E2.** Have you had any new haemorrhoid operations since your operation for haemorrhoids approximately one year ago? Yes ☐ No ☐

If Yes, please specify:

Operation 1:

Type: _____

Month (e.g. June): _____

Total nights admitted to hospital

Operation 2:

Type: _____

Month (e.g. June): _____

Total nights admitted to hospital

- E3.** Since your haemorrhoid surgery one year ago, have you been re-admitted to hospital for any other reason, in relation to your haemorrhoids surgery? Yes ☐ No ☐

If Yes to question E3, how many nights were you readmitted in total?

- E4.** *If Yes to question E3, why were you readmitted? (Please give details):*

- E5.** Have you visited hospital outpatients to see a doctor, in relation to your haemorrhoids, in the last year? Yes ☐ No ☐

If Yes to question E5, how many times did you visit outpatients?

- E6. Have you seen your GP, in relation to your haemorrhoids, in the last year?** Yes ☐ No ☐

If Yes to question E6, how many times did you see your GP?

- E7. Have you seen a practice nurse, in relation to your haemorrhoids, in the last year?** Yes ☐ No ☐

If Yes to question E7, how many times did you see the nurse?

- E8. Have you visited any other health care professional, in relation to your haemorrhoids, in the last year?** Yes ☐ No ☐

If Yes to question E8, please specify whom you have seen, and the number of times you have seen them, in the boxes provided:

Seen by (please specify):

Times

- E9. Were you prescribed any medicines by a doctor or nurse in relation to your haemorrhoids symptoms, in the last year? (eg medication to relieve haemorrhoids symptoms such as itching or bleeding)?** Yes ☐ No ☐

If Yes, please provide details:

- E10. Did you buy any medicines over the counter to treat your haemorrhoids symptoms in the last year?** Yes ☐ No ☐

- E11. If Yes to E10 above, how much in total did you spend?**

£

- E12. Did you pay to see any private health care professional, in relation to your haemorrhoids, in the last year?** Yes ☐ No ☐

- E13. Have you paid for any other health care, in relation to your haemorrhoids, in the last year?** Yes ☐ No ☐

- E14. If Yes to questions E12 or E13, how much did you spend?**

£

- E15. Are you in paid employment?** Yes ☐ No ☐

- E16.** *If Yes to question E15, how many days off sick have you had in the last year because of problems relating to your haemorrhoids?*

Thank you very much for being part of the eTHoS study and 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.

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Aberdeen
AB25 2ZD

Tel: [REDACTED]

E-mail: [REDACTED]
[REDACTED]

Study No

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PARTICIPANT QUESTIONNAIRE

2 YEARS
since you joined

CONFIDENTIAL

Thank you for helping us with our research.
It is now approximately 2 years since you first joined the eTHoS study.
We would be very grateful if you could complete this questionnaire.

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 2.3, October 2012

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 cross (x) 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 questionnaire filled in

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

SECTION A: DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

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 some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some 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 with performing my usual activities	☐
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	I am unable to perform my usual activities	☐
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	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

[Section B: Your General Health (SF-36©) has been removed due to copyright]

SECTION C: ASSESSMENT OF FAECAL (STOOL) INCONTINENCE

This set of questions asks about faecal (stool) incontinence. Can you please mark with an X in the appropriate box if you have experienced any of the following in the past 4 weeks:

	Always	Often	Sometimes	Rarely	Never
C1. Incontinence of solid stool	☐	☐	☐	☐	☐
C2. Incontinence of liquid stool	☐	☐	☐	☐	☐
C3. Incontinence of gas	☐	☐	☐	☐	☐
C4. Need to wear a pad or plug	☐	☐	☐	☐	☐
C5. Altered your lifestyle	☐	☐	☐	☐	☐

"always" = one or more times daily, "often" = more than once a week but less than once daily; "sometimes" = more than once a month but less than once a week; "rarely" = less than once a month.

SECTION D: HAEMORRHOIDS SYMPTOM SCORE

This set of questions asks you about any symptoms related to haemorrhoids that you have had in the past 4 weeks. Please mark an X in the appropriate box.

	None	Spotting	Staining underwear	Dripping into pan	Without stool
D1. Any bleeding from your back passage?	☐	☐	☐	☐	☐
	None	Only with stool	Constant throbbing		
D2. Any pain in your back passage?	☐	☐	☐		
D3. Do you have any of the following other symptoms:					
	Always	Often	Sometimes	Rarely	Never
a) Prolapse (a sensation of something coming down out of your back passage)	☐	☐	☐	☐	☐
b) Itching	☐	☐	☐	☐	☐
c) Mucous discharge	☐	☐	☐	☐	☐
d) Faecal urgency (unable to defer defecation for 15 mins)	☐	☐	☐	☐	☐
e) Faecal frequency (more often than before you had haemorrhoids)	☐	☐	☐	☐	☐

- Always Often Sometimes Rarely Never
- D4.** Have you suffered with tenesmus (a constant sensation in your back passage, which gives you an urge to move your bowel)? ☐ ☐ ☐ ☐ ☐

SECTION E: HOW ARE YOU KEEPING

- E1.** Have your haemorrhoids come back at all in the last year? Yes ☐ No ☐
- E2.** Have you had any new haemorrhoid operations in the last year? Yes ☐ No ☐

If Yes, please specify:

Operation 1:

Type: _____

Month (e.g. June): _____

Total nights admitted to hospital

Operation 2:

Type: _____

Month (e.g. June): _____

Total nights admitted to hospital

- E3.** Have you been re-admitted to hospital for any other reason in the last year, in relation to your haemorrhoids surgery? Yes ☐ No ☐

If Yes to question E3, how many nights were you readmitted in total?

- E4.** *If Yes to question E3, why were you readmitted? (Please give details):*

- E5.** Have you visited hospital outpatients to see a doctor, in relation to your haemorrhoids, in the last year? Yes ☐ No ☐

If Yes to question E5, how many times did you visit outpatients?

- E6.** Have you seen your GP, in relation to your haemorrhoids, in the last year? Yes ☐ No ☐

If Yes to question E6, how many times did you see your GP?

- E7.** Have you seen a practice nurse, in relation to your haemorrhoids, in the last year?

Yes ☐ No ☐

If Yes to question E7, how many times did you see the nurse?

- E8.** Have you visited any other health care professional, in relation to your haemorrhoids, in the last year?

Yes ☐ No ☐

If Yes to question E8, please specify whom you have seen, and the number of times you have seen them, in the boxes provided:

Seen by (please specify):

Times

- E9.** Were you prescribed any medicines by a doctor or nurse, in relation to your haemorrhoids symptoms, in the last year? (eg medication to relieve haemorrhoids symptoms such as itching or bleeding)?

Yes ☐ No ☐

If Yes, please provide details:

- E10.** Did you buy any medicines over the counter to treat your haemorrhoids symptoms in the last year?

Yes ☐ No ☐

- E11.** If Yes to E10 above, how much in total did you spend?

£

- E12.** Did you pay to see any private health care professional, in relation to your haemorrhoids, in the last year?

Yes ☐ No ☐

- E13.** Have you paid for any other health care, in relation to your haemorrhoids, in the last year?

Yes ☐ No ☐

- E14.** If Yes to questions E12 or E13, how much did you spend?

£

- E15.** Are you in paid employment?

Yes ☐ No ☐

- E16.** If Yes to question E15, how many days off sick have you

had in the last year because of problems relating to your haemorrhoids?

Thank you very much for being part of the eTHoS study and 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.

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Tel: [REDACTED]
E-mail: [REDACTED]
[REDACTED]

Study No

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PARTICIPANT QUESTIONNAIRE

TREATMENT CHOICE

Block 1

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 1, August 2015

Guidance notes

Haemorrhoid treatments and their outcomes

We are interested in your views and opinions about how haemorrhoids (piles) are treated.

Treatments for haemorrhoids:

There are 3 types of surgery. All surgical treatments are commonly performed under general anaesthetic (you are completely asleep) as a hospital day-case or inpatient admission by trained colorectal surgeons and, in general, all are successful in improving patients symptoms with little risk but there are differences in the way they are performed.

Excisional Haemorrhoidectomy

Excisional haemorrhoidectomy involves gently opening the anus and cutting away the haemorrhoid (piles) swellings in order to improve symptoms. The wounds can either be left open to heal or are closed with stitches.

Haemorrhoidal Artery Ligation

Haemorrhoidal Artery Ligation uses a surgical instrument (a Doppler probe) to locate haemorrhoidal (piles) arteries so they can be tied off internally with a dissolving stitch (suture) to block the blood supply to the artery.

Stapled Haemorrhoidopexy

Stapled haemorrhoidopexy surgery involves cutting away a ring or donut of tissue above the swellings and special staples are used to join the tissue again. The staples remain on the inside and you should not be aware of them.

In this survey we would like to understand what people think about these different treatments. When completing the questionnaire, you will be presented with a number of choices which ask you to choose between three different treatment options: Excisional; Artery ligation; and Stapled. You will also have the option of choosing no treatment. These treatment options will involve different levels of the following factors:

Time in post operative pain

This describes the number of days in which you are in pain during the first six weeks after your operation. This is pain that requires taking painkillers for relief. For example, the pain may last for:

3 days which means that you have to take painkillers for these days

7 days

21 days

30 days

Chance of serious complications requiring hospitalisation

This refers to complications/side effects of the treatment of that could lead to visit to health care provider such as Accidents and Emergency visits or spending a few days in hospital. These complications could include: severe bleeding/haemorrhage; abscess after operation; infection; urinary or faecal incontinence.

For example, the chance might be that:

10 in 1000 (1.0%) people receiving treatment for haemorrhoids will have serious complications
 15 in 1000 (1.5%)
 20 in 1000 (2.0%)
 30 in 1000 (3.0%)

Time taken to return to usual activities

This describes the time that it may take you to return to your usual activities such as work, housekeeping, leisure or studying. For example, in:

3 days you would have returned to work or,
 21 days
 30 days
 42 days

Chance of a recurrence of haemorrhoidal symptoms

This describes the chance that in 12 months time your symptoms you had before your surgery might come back. These symptoms include minor bleeding, itching, pain and skin tags. For example:

9 in 1000 people (0.9%) symptoms come back, or
 15 in 1000 people (1.5%)
 18 in 1000 people (1.8%)
 21 in 1000 people (2.1%)

Cost of treatment

This refers to how much you would value the surgical interventions. One way of finding out your value is to find out how much you would be willing to pay for such a service. Please consider what you would be personally willing and able to pay for the service you choose. Remember that any money you spend on this service will not be available to spend on other things.

- £100 cost per treatment
- £200 cost per treatment
- £300 cost per treatment
- £400 cost per treatment

ISRCTN80061723

Version 1, August 2015

Example Choice Question

When answering these questions we would like you to IMAGINE that you have haemorrhoids causing symptoms of bleeding, pain or itching. These symptoms have not been resolved by either the advice the doctor gave you or simple treatments such as creams or rubber band ligation. The surgeon has offered you surgery to resolve your symptoms. For each choice below please indicate which option you would choose by putting a TICK in the appropriate box.

In this section you will be presented with 8 choices, each offering four treatment options: (1) excisional haemorrhoidectomy (Excisional), (2) haemorrhoidal artery ligation (Artery ligation), (3) stapled haemorrhoidopexy (Stapled) and (4) no treatment.

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	7 days	21 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	30 in 1000 people (3%)	10 in 1000 people (1%)	
Time taken to return to usual activities	21 days	30 days	42 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	15 in 1000 people (1.5%)	18 in 1000 people (1.8%)	
Cost of treatment	£300	£400	£200	

Which treatment would you choose

Excisional	Artery ligation	Stapled	No treatment
☒	☐	☐	☐

The person would choose Excisional treatment that has 7 days post operative pain, 20 in 1000 chance of serious complications requiring hospitalisation, 21 days taken to return to usual activities 21 in 1000 chance of recurrence of haemorrhoidal symptoms and a treatment cost of £300. This person prefers Excisional treatment to Artery ligation, Stapled or no treatment.

ISRCTN80061723

Version 1, August 2015

Section 1: Treatment choice

Please remember there is no right or wrong answer. We just want to know what **YOU** think.

Choice 1: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	30 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people	30 in 1000 people (3%) (3%)	15 in 1000 people (1.5%)	
Time taken to return to usual activities	30 days	42 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	18 in 1000 people (1.8%)	21 in 1000 people (2.1%)	15 in 1000 people (1.5%)	
Cost of treatment	£300	£400	£200	
I would choose (Please tick one box only)				

Choice 2: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	21 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	30 in 1000 people	20 in 1000 people (2%)	
Time taken to return to usual activities	42 days	21 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	18 in 1000 people (1.8%)	9 in 1000 people (0.9%)	15 in 1000 people (1.5%)	
Cost of treatment	£400	£200	£100	
I would choose (Please tick one box only)				

Choice 3: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	30 days	21 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	10 in 1000 people (1%)	20 in 1000 people	
Time taken to return to usual activities	42 days	30 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	
Cost of treatment	£300	£400	£200	
I would choose (Please tick one box only)				

Choice 4: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	30 days	21 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	10 in 1000 people (1%)	15 in 1000 people (1.5%)	
Time taken to return to usual activities	30 days	21 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	18 in 1000 people (1.8%)	21 in 1000 people (2.1%)	
Cost of treatment	£200	£300	£400	
I would choose (Please tick one box only)				

Choice 5: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	30 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	15 in 1000 people (1.5%)	30 in 1000 people (3%)	
Time taken to return to usual activities	42 days	30 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	
Cost of treatment	£100	£200	£400	
I would choose (Please tick one box only)				

Choice 6: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	7 days	3 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	20 in 1000 people (2%)	15 in 1000 people (1.5%)	
Time taken to return to usual activities	21 days	3 days	42 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	
Cost of treatment	£100	£200	£300	
I would choose (Please tick one box only)				

Choice 7: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	7 days	21 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	10 in 1000 people (1%)	30 in 1000 people (3%)	
Time taken to return to usual activities	42 days	30 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	18 in 1000 people (1.8%)	21 in 1000 people (2.1%)	9 in 1000 people (0.9%)	
Cost of treatment	£400	£300	£200	
I would choose (Please tick one box only)				

Choice 8: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	30 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	20 in 1000 people (2%)	10 in 1000 people (1%)	
Time taken to return to usual activities	21 days	3 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	
Cost of treatment	£200	£100	£300	
I would choose (Please tick one box only)				

Section 2: About yourself

So we can understand better your answers to the previous questions, we would like to ask a few questions about yourself.

1. Which of these qualifications do you have?	
Please tick (✓) every box that applies if you have any of the qualifications.	
1-4 O levels/CSEs/GCSEs (any grades), O Grades, Standard Grades, Entry Level, Foundation Diploma, Access 3 Cluster, Intermediate 1 or 2, Senior Certificate or equivalent	
NVQ/SVQ Level 1 or 2, GNVQ/ GSVQ Foundation or Intermediate, Basic Skills, SCOTVEC Module, BTEC First/General Diploma, RSA Diploma, City and Guilds Craft or equivalent	
5+ O levels (passes)/CSEs (grade1)/GCSEs (grades A*-C), School Certificate, 1 A level /2-3 AS levels/VCEs, Higher Diploma or equivalent	
Apprenticeship	
2+ A levels/VCEs, 4+ AS Levels, Scottish Highers, Advanced Highers or CSYS, Higher School Certificate, Progression/Advanced Diploma, Advanced Senior Certificate or equivalent	
NVQ/SVQ Level 3, Advanced GNVQ/GSVQ, City and Guilds Advanced Craft, ONC, OND, BTEC national, SCOTVEC National diploma, RSA Advanced Diploma or equivalent	
Degree (for example BA, BSc), Higher degree/Postgraduate qualifications (for example MA, PhD, PGCE), NVQ / SVQ Level 4-5, HNC, HND, RSA Higher Diploma, BTEC Higher Level or equivalent	
Professional qualifications (for example teaching, nursing, accountancy)	
Other qualifications (including school, post-school, higher education and vocational / work-related)	
Foreign qualifications	
No qualifications	
Prefer not to say	

2. Last week, were you: Please include any work, including casual or temporary, even if only for one hour. (Please tick (✓) all that apply.)		
Working as an employee?	Actively looking for a job?	
Self-employed or freelance?	Unemployed?	
On a Government sponsored training scheme?	Retired (whether receiving a pension or not)?	
Working paid or unpaid for your own or your family's business?	A student?	
Away from work ill, maternity leave, on holiday or temporarily laid off?	Looking after home or family?	
Doing any other kind of paid work?	Long-term sick or disabled?	
Other (Please tick and write in the box.)		

3. Which group represents your total income including any benefits received and before any deductions? (Please tick (✓) either weekly or annual income.)

Up to £99 per week (up to £5,199 per year)	
£100 and up to £199 per week (£5,200 and up to £10,399 per year)	
£200 and up to £299 per week (£10,400 and up to £15,599 per year)	
£300 and up to £399 per week (£15,600 and up to £20,799 per year)	
£400 and up to £499 per week (£20,800 and up to £25,999 per year)	
£500 and up to £599 per week (£26,000 and up to £31,199 per year)	
£600 and up to £699 per week (£31,200 and up to £36,399 per year)	
£700 and up to £999 per week (£36,400 and up to £51,999 per year)	
£1000 and above per week (£52,000 and above per year)	
Prefer not to say	

Are there any comments that you would like to make regarding the questionnaire?

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

**Please send the questionnaire back to us in Aberdeen
in the prepaid envelope provided.**

**If you would like any further information or have any queries about the study,
please contact:**

eTHoS Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD

Tel: [REDACTED]

E-mail: [REDACTED]
[REDACTED]

ISRCTN80061723

Version 1, August 2015

Study No

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PARTICIPANT QUESTIONNAIRE

TREATMENT CHOICE

Block 2 – Section 1

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 1, August 2015

Section 1: Treatment choice

Please remember there is no right or wrong answer. We just want to know what **YOU** think.

Choice 1: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	21 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	15 in 1000 people (1.5%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	21 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	21 in 1000 people (2.1%)	
Cost of treatment	£300	£100	£200	
I would choose (Please tick one box only)				

Choice 2: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	7 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	15 in 1000 people (1.5%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	3 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	9 in 1000 people (0.9%)	15 in 1000 people (1.5%)	
Cost of treatment	£200	£300	£400	
I would choose (Please tick one box only)				

ISRCTN80061723

Version 1, August 2015

Choice 3: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	7 days	30 days	21 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	20 in 1000 people (2%)	30 in 1000 people (3%)	
Time taken to return to usual activities	42 days	21 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	18 in 1000 people (1.8%)	9 in 1000 people (0.9%)	15 in 1000 people (1.5%)	
Cost of treatment	£200	£400	£300	
I would choose (Please tick one box only)				

Choice 4: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	30 days	3 days	21 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	15 in 1000 people (1.5%)	30 in 1000 people (3%)	
Time taken to return to usual activities	21 days	30 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	21 in 1000 people (2.1%)	15 in 1000 people (1.5%)	
Cost of treatment	£400	£100	£300	
I would choose (Please tick one box only)				

Choice 5: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	7 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	10 in 1000 people (1%)	20 in 1000 people (2%)	
Time taken to return to usual activities	30 days	42 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	18 in 1000 people (1.8%)	9 in 1000 people (0.9%)	
Cost of treatment	£100	£200	£400	
I would choose (Please tick one box only)				

Choice 6: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	30 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	10 in 1000 people (1%)	20 in 1000 people (2%)	
Time taken to return to usual activities	30 days	21 days	42 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	18 in 1000 people (1.8%)	9 in 1000 people (0.9%)	
Cost of treatment	£200	£300	£100	
I would choose (Please tick one box only)				

Choice 7: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	7 days	21 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	30 in 1000 people (3%)	15 in 1000 people (1.5%)	
Time taken to return to usual activities	42 days	3 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	
Cost of treatment	£200	£300	£100	
I would choose (Please tick one box only)				

Choice 8: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	30 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	10 in 1000 people (1%)	20 in 1000 people (2%)	
Time taken to return to usual activities	42 days	3 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	21 in 1000 people (2.1%)	15 in 1000 people (1.5%)	
Cost of treatment	£300	£200	£400	
I would choose (Please tick one box only)				

Study No

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PARTICIPANT QUESTIONNAIRE

TREATMENT CHOICE

Block 3 – Section 1

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 1, August 2015

Section 1: Treatment choice

Please remember there is no right or wrong answer. We just want to know what **YOU** think.

Choice 1: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	21 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	20 in 1000 people (2%)	15 in 1000 people (1.5%)	
Time taken to return to usual activities	3 days	30 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	
Cost of treatment	£100	£300	£200	
I would choose (Please tick one box only)				

Choice 2: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	7 days	30 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	30 in 1000 people (3%)	10 in 1000 people (1%)	
Time taken to return to usual activities	3 days	30 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	
Cost of treatment	£300	£100	£400	
I would choose (Please tick one box only)				

Choice 3: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	3 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	20 in 1000 people (2%)	30 in 1000 people (3%)	
Time taken to return to usual activities	42 days	21 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	18 in 1000 people (1.8%)	
Cost of treatment	£100	£300	£400	
I would choose (Please tick one box only)				

Choice 4: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	30 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	30 in 1000 people (3%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	30 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	
Cost of treatment	£200	£100	£400	
I would choose (Please tick one box only)				

Choice 5: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	30 days	7 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	15 in 1000 people (1.5%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	21 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	15 in 1000 people (1.5%)	9 in 1000 people (0.9%)	
Cost of treatment	£400	£200	£100	
I would choose (Please tick one box only)				

Choice 6: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	21 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	15 in 1000 people (1.5%)	20 in 1000 people (2%)	
Time taken to return to usual activities	30 days	3 days	42 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	9 in 1000 people (0.9%)	
Cost of treatment	£200	£400	£100	
I would choose (Please tick one box only)				

Choice 7: Please compare the treatments and tick (✓) the treatment, if any, you would choose				
	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	30 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	20 in 1000 people (2%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	3 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	
Cost of treatment	£400	£100	£300	
I would choose (Please tick one box only)				

Choice 8: Please compare the treatments and tick (✓) the treatment, if any, you would choose				
	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	7 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	15 in 1000 people (1.5%)	30 in 1000 people (3%)	
Time taken to return to usual activities	42 days	3 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	
Cost of treatment	£200	£300	£100	
I would choose (Please tick one box only)				

Study No

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PARTICIPANT QUESTIONNAIRE

TREATMENT CHOICE

Block 4 – Section 1

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 1, August 2015

Section 1: Treatment choice

Please remember there is no right or wrong answer. We just want to know what **YOU** think.

Choice 1: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	30 days	7 days	21 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	30 in 1000 people (3%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	21 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	9 in 1000 people (0.9%)	
Cost of treatment	£300	£100	£400	
I would choose (Please tick one box only)				

Choice 2: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	30 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	15 in 1000 people (1.5%)	20 in 1000 people (2%)	
Time taken to return to usual activities	42 days	30 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	9 in 1000 people (0.9%)	21 in 1000 people (2.1%)	
Cost of treatment	£100	£200	£300	
I would choose (Please tick one box only)				

ISRCTN80061723

Version 1, August 2015

Section 1: Treatment choice

Please remember there is no right or wrong answer. We just want to know what **YOU** think.

Choice 1: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	30 days	7 days	21 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	30 in 1000 people (3%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	21 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	9 in 1000 people (0.9%)	
Cost of treatment	£300	£100	£400	
I would choose (Please tick one box only)				

Choice 2: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	30 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	15 in 1000 people (1.5%)	20 in 1000 people (2%)	
Time taken to return to usual activities	42 days	30 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	15 in 1000 people (1.5%)	9 in 1000 people (0.9%)	21 in 1000 people (2.1%)	
Cost of treatment	£100	£200	£300	
I would choose (Please tick one box only)				

ISRCTN80061723

Version 1, August 2015

Choice 3: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	7 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	10 in 1000 people (1%)	30 in 1000 people (3%)	20 in 1000 people (2%)	
Time taken to return to usual activities	30 days	21 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	21 in 1000 people (2.1%)	18 in 1000 people (1.8%)	
Cost of treatment	£400	£100	£200	
I would choose (Please tick one box only)				

Choice 4: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	21 days	7 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	15 in 1000 people (1.5%)	20 in 1000 people (2%)	10 in 1000 people (1%)	
Time taken to return to usual activities	21 days	30 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	21 in 1000 people (2.1%)	
Cost of treatment	£100	£400	£200	
I would choose (Please tick one box only)				

Choice 5: Please compare the treatments and tick (✓) the treatment, if any, you would choose				
	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	30 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	15 in 1000 people (1.5%)	30 in 1000 people (3%)	
Time taken to return to usual activities	21 days	30 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	
Cost of treatment	£300	£200	£400	
I would choose (Please tick one box only)				

Choice 6: Please compare the treatments and tick (✓) the treatment, if any, you would choose				
	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	30 days	21 days	3 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	20 in 1000 people (2%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	30 days	3 days	
Chance of a recurrence of haemorrhoidal symptoms	21 in 1000 people (2.1%)	18 in 1000 people (1.8%)	9 in 1000 people (0.9%)	
Cost of treatment	£400	£300	£100	
I would choose (Please tick one box only)				

Choice 7: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	7 days	21 days	30 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	20 in 1000 people (2%)	15 in 1000 people (1.5%)	10 in 1000 people (1%)	
Time taken to return to usual activities	42 days	3 days	21 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	21 in 1000 people (2.1%)	18 in 1000 people (1.8%)	
Cost of treatment	£100	£400	£300	
I would choose (Please tick one box only)				

Choice 8: Please compare the treatments and tick (✓) the treatment, if any, you would choose

	Excisional	Artery ligation	Stapled	No treatment
Time in post-operative pain	3 days	21 days	7 days	If you do not seek treatment your symptoms will persist and possibly become worse
Chance of serious complications requiring hospitalisation	30 in 1000 people (3%)	15 in 1000 people (1.5%)	20 in 1000 people (2%)	
Time taken to return to usual activities	42 days	21 days	30 days	
Chance of a recurrence of haemorrhoidal symptoms	9 in 1000 people (0.9%)	18 in 1000 people (1.8%)	15 in 1000 people (1.5%)	
Cost of treatment	£200	£300	£100	
I would choose (Please tick one box only)				

Study No

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PARTICIPANT COSTS QUESTIONNAIRE

CONFIDENTIAL

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

This study is funded by the
NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre,
Health Technology Assessment programme (NETSCC HTA)

ISRCTN80061723

Version 1.1, March 2012

This questionnaire will help us to find out how much it costs you to use health services. In relation to your haemorrhoid symptoms, we wish to ask about your most recent admission to hospital, your most recent outpatient appointment and your most recent appointment with a GP. We wish to know how much money and time were spent by you and any companion in attending these appointments and as a result of any hospital admission you may have had.

It may have been a long time ago and we understand that you are unlikely to remember the exact details. Please just give us your best guess.

If you have a problem in answering any question please telephone the eTHoS Study Office on [REDACTED]. Please return the questionnaire in the enclosed pre-paid envelope. Thank you very much for taking the time to answer this questionnaire.

SECTION A: YOUR MOST RECENT ADMISSION TO HOSPITAL

If, in the last 18 months, you were not admitted to hospital due to your haemorrhoid symptoms, please go to Section B.

A1. Please circle the number that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

Bus	1	Ambulance	5
Train	2	Private car	6
Taxi	3	Other (please specify below)	7
Hospital car	4		

A2. If you travelled by bus, train or taxi to hospital what was the total cost of the (one-way) journey? Please write the cost in the box below. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare.

Cost of (one-way) fare (£) - pence

A3. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.

Number of miles one-way

A4. If you travelled by private car and you or your companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay a parking fee.

Expenditure on parking fee (£) - pence

- A5. When you were admitted to the hospital, how long did you spend there?
Please write the number of days in the box below.**

Number of days

--	--

- A6. What would you otherwise have been doing as your main activity if you had not had to be admitted to hospital? Please circle the number that best applies to you.**

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4	Other (please specify below)	8

- A7. When you were admitted to hospital, did anyone come with you?**

Yes (continue to question 8)	1
No (go to Section B)	2

- A8. Who accompanied you to the hospital? Please circle the number that best describes the main person who accompanied you to the hospital.**

Partner/spouse	1	Friend	4
Other relative	2	Other (please specify below)	5
Paid caregiver	3		

A9. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to the hospital.

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4	Other (please specify below)	8

A10. Did your main companion take time off from paid work (or business activity if self-employed)?

Yes (continue to question 11)	1
No (go to section B)	2

A11. Please write the number of hours your companion took off from paid work (or business activity if self-employed) in the box below. Please put zero if your main companion did not take time off from paid work (or business activity if self-employed) to accompany you to the hospital.

Number of hours

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A12. Whilst you were in hospital, approximately how many times did your main companion come to visit you?

Number of times

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SECTION B: YOUR MOST RECENT OUTPATIENT VISIT

If, in the last 18 months, you did not have an outpatient's appointment about your haemorrhoid symptoms, please go to Section C.

- B1. Please circle the number that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.**

Bus	1	Ambulance	5
Train	2	Private car	6
Taxi	3	Other (please specify below)	7
Hospital car	4		

- B2. If you travelled by bus, taxi or train to hospital what was the total cost of the (one-way) journey? Please write the cost in the box below. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare.**

Cost of (one-way) fare (£) - pence

- B3. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.**

Number of miles one-way

- B4. If you travelled by private car and you or your companion had to pay a parking fee, approximately how much did this cost? Please write the cost in the box below. Please put zero if you did not pay a parking fee.**

Expenditure on parking fee (£) - pence

- B5. When you visited outpatients, how long did it take to travel there? Please write the number of hours and minutes in the box below.**

Number of hours – minutes

- B6. When you visited outpatients, how long did you spend there? Please write the number hours and minutes in the box below.**

Number of hours – minutes

- B7. Please circle the number that best describes what you otherwise would have been doing as your main activity if you had not been visiting outpatients?**

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4	Other (please specify below)	8

- B8. When you visited outpatients did anyone come with you?**

Yes (continue to question 9)	1
No (go to section C)	2

- B9. Please circle the number that best describes the main person who accompanied you to outpatients.**

Partner/spouse	1	Friend	4
Other relative	2	Other (please specify below)	5
Paid caregiver	3		

B10. If your main companion travelled with you by bus or train approximately how much did they pay (one-way) in fares? Please write the approximate cost in the box below. Please put zero if your main companion did not travel by bus or train at all.

Cost of (one-way) fare (£) – pence

B11. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to outpatients.

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4	Other (please specify below)	8

SECTION C: YOUR MOST RECENT GP APPOINTMENT (DUE TO YOUR HAEMORROIDS)

C1. Please circle the number that best describes how you travelled to your most recent GP appointment about your haemorrhoid symptoms. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

Walked	1	Bus	4
Cycled	2	Taxi	5
Private car	3	Other (please specify below)	6

- C2. If you travelled by bus or taxi, what was the cost of the (one-way) fare? Please write the cost in the box below. Please put zero if you did not travel by bus or taxi or if you did not pay the fare.

Cost of (one-way) fare (£) – pence

- C3. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.

Number of miles one-way

- C4. If you travelled by private car and you or a companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay for parking.

Expenditure on parking fee (£) – pence

- C5. When you visited the GP, how long did it take to travel there? Please write the number of minutes in the box below.

Number of minutes

- C6. When you visited the GP, how long did you spend there? Please write the number minutes in the box below. Please include in your answer the time spent waiting and also the time spent with the doctors and nurses

Number of minutes

- C7. Please cross the box that best describes what you otherwise would have been doing as your main activity if you had not visited the GP.

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4	Other (please specify below)	8

C8. When you visited the GP did anyone come with you?

Yes	Yes(continue to question 9)	1
No	(go to the end)	2

C9. Please circle the number(s) that best describe the person(s) who accompanied you to the GP surgery.

Partner/spouse	1	Friend	4
Other relative	2	Other (please specify below)	5
Paid caregiver	3		

C10. If your main companion travelled with you by bus how much approximately did they pay (one-way) in fares (if anything)? Please write the cost in the box below. Please put zero if your main companion did not travel by bus at all.

Cost of (one-way) fare (£)

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 –

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 pence

C11. Please cross the box that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to the GP's surgery.

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4	Other (please specify below)	8

Thank you very much for being part of the eTHoS 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.

Please send the questionnaire back to us in Aberdeen in the prepaid envelope provided.

If you would like any further information or have any queries about the study, please contact:

eTHoS Trial Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
Health Science Building
Foresterhill
Aberdeen
AB25 2ZD
Tel: [REDACTED]
Fax: [REDACTED]
E-mail: [REDACTED]

Appendix 2 The eTHoS study patient information sheet



The eTHoS Study (either Traditional Haemorrhoidectomy or Stapled Haemorrhoidopexy)

PATIENT INFORMATION LEAFLET

INVITATION TO TAKE PART

You are being invited to take part in a research study. We would like you to take a little time to decide if you would like to take part. Before you do decide, it is important that you understand why the research is being done and what taking part will involve. Please take time to read this information leaflet carefully and you can discuss it with friends, relatives and your GP. If the information is not clear or if you would like more information, please ask us. Contact details are at the end of the leaflet.

WHY HAVE I BEEN INVITED TO TAKE PART?

You have been chosen because you are suitable for this study. You have haemorrhoids and you have been told that surgical treatment is required to improve your symptoms. We hope that approximately 800 patients will take part and complete this study in the UK.

DO I HAVE TO TAKE PART?

No and you do not have to decide today. You have been given this information sheet to take home and you can read it as many times as you wish and ask as many questions as you need to before you make a decision.

If you decide that you do not want to take part in the study now or wish to withdraw at a later stage, this will not affect the standard of care you receive.

If you decide to take part, you will be asked to sign a "consent form" before your participation in the study begins. However, even after you have signed this form, you are still free to withdraw at any time and without giving a reason.

BACKGROUND TO THE CONDITION

Haemorrhoids are swellings around the back passage which can cause bleeding, pain and itching and can protrude. When they become enlarged, surgery is often advised as it is an effective way to control the symptoms.

There are two major surgical treatments for haemorrhoids; "traditional" surgery and a surgical treatment in which the haemorrhoids are "stapled".

ISRCTN80061723

Version 2.1 December 2011

What is the current ('traditional') surgical treatment for haemorrhoids?

Traditional surgery involves removal of the swellings in order to improve symptoms. This traditional approach is effective; however it is often associated with immediate post operative pain.

What is the "stapled" surgical treatment?

Newer surgical techniques include "stapled" treatment. The surgery involves cutting away a ring or 'donut' of tissue above the swellings and special staples are used to join the tissue again. Its advantages include a possible reduction of pain immediately after surgery, shorter operating time and hospital stay and a quicker return to work. However, over the longer term patients who have this type of surgery may be more likely to experience haemorrhoids again and need further surgery.

Both surgical treatments are commonly performed as a hospital day-case or inpatient admission by colorectal surgeons and, in general, both are successful in improving patients' symptoms.

WHAT IS THE PURPOSE OF THE STUDY?

At present there is no evidence that tells us which of these types of surgery is best for patients like you who have haemorrhoids that require surgery. The eTHoS study will investigate which of the two surgeries is the best surgical treatment for different kinds of patients.

HOW WILL WE DO THIS?

Patients who agree to take part in the eTHoS study will be divided into two separate treatment groups (see below). The type of treatment patients receive will depend on which group they are in. The researchers will then compare the general health and quality of life of the people in these two treatment groups over the same amount of time.

Group number	Group name	Group treatment
Group 1	Traditional surgical treatment group	This group will receive traditional surgery for haemorrhoidal disease
Group 2	Stapled surgical treatment group	This group will receive stapled surgery for haemorrhoidal disease

The treatment group that you are put in will be decided at random. This means that neither you nor the doctors will be able to decide which surgical treatment you will receive. This method is used to make sure that the groups of patients who receive the two types of treatment are very similar. Because we do not know which treatment is best, everyone has an equal (50/50) chance of receiving the treatment that is shown to be most effective once the study is completed. To take part in this study you must be happy to be in either of the treatment groups.

HAVE ANY STUDIES LIKE THIS BEEN DONE BEFORE?

Yes. There are several studies that have shown that haemorrhoidal symptoms improve after either type of surgery. However, many of the studies did not follow patients up for long enough afterwards and there is still uncertainty about which type of surgery is most likely to be followed by complications or by more haemorrhoids and a need for further surgery.

Therefore, the eTHoS study is important because it will be the first major study to address all these issues. By participating in the eTHoS study you will be helping to improve our knowledge and this will help us to treat patients with haemorrhoids in the future.

WHAT WILL HAPPEN NEXT?

1) *You are being asked to consider taking part in the study*

You will have been given this information sheet by your surgeon. Your surgeon will be able to answer any questions and discuss with you any aspect of the study during your consultation appointment. During your appointment you will be asked if you would like to take part in the study or if you need more time to consider your decision. You can keep this information sheet and can re-read through the information at home in detail.

2) *What will happen if I am ready to make a decision?*

If you are happy to agree to take part in the study during your appointment, you will be asked to sign a consent form. You will then be asked to complete a questionnaire about your health in general and your haemorrhoidal symptoms such as pain and incontinence. Each questionnaire should take approximately 15 - 20 minutes to complete. After completion of the questionnaire and prior to your surgery you will be assigned by the telephone or computer system (at random) to one of the two treatment groups. If you wish, your surgeon can inform you of the group you have been placed in, once this is known.

3) *What will happen if I am not ready to make a decision today?*

You will be approached at your next appointment or when admitted before your operation in order to receive your final response and answer any other questions you may have. If you have any questions before your next appointment please feel free to contact your local research nurse or the central office (contact details are at the end of this leaflet).

4) *What happens next?*

If you decide to take part, you will be placed on the surgery waiting list for the type of surgery you have been randomised to (either traditional or stapled surgery). You are likely to undergo your surgery within approximately two months (from the time of randomisation) but this will vary in different hospitals. There will be the same time to wait for your operation, whether you join the study or not.

Precise procedures for surgery vary. The surgery may be done as a day case or you may have to stay overnight. You may receive a general or local anaesthetic. Your surgeon will discuss these things with you.

After your surgery you will receive an outpatient clinic appointment to return to the hospital to check how you are getting on. If your haemorrhoidal symptoms are still not adequately controlled you may receive further treatment. You will receive an appointment to come back to hospital whether or not you take part in the trial.

IF I PARTICIPATE IN THE STUDY WHAT WILL HAPPEN AFTER MY SURGERY?

The study will collect information from all the patients who take part in the study for five years after surgery. In research this is called "follow up". Everyone in the study will be followed up in exactly the same way. If you take part in the study you will return to the clinic at the hospital approximately 6 weeks after your operation. You will also be sent questionnaires from the central co-ordinating office in Aberdeen at approximately 1, 3 and 6 weeks and 12, 24 and 60 months after your operation. You will be sent a reply-paid envelope to return the questionnaire.

ARE THERE POSSIBLE BENEFITS TO ME OF TAKING PART?

You will receive proper health care by your consultant whether you choose to participate in the study or not. There is no guarantee that either type of surgery will be better for you than the other.

eTHoS is an important study because if either surgery is found likely to be more beneficial than the other, this will become the treatment of choice for people with haemorrhoids. By taking part in this

study you will be directly helping us to inform the treatment of future patients diagnosed with haemorrhoids that need surgical treatment.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

1) *The Stapled surgical treatment group*

The chance of having haemorrhoidal symptoms again in the future may be higher than with traditional surgery.

2) *The Traditional surgical treatment group*

Potential disadvantages/risks may include more post-operative pain, but this can usually be resolved with pain-reducing drugs.

At present surgeons do not know if the risk of having a complication after surgery, such as bleeding, requirement of blood transfusion, anal stenosis or fissure, urinary retention, incontinence, wound or pelvic infection is higher with one of these two procedures.

WHAT IF THERE IS A PROBLEM?

We do not believe that by taking part in this study there is any greater risk of harm than if you have surgery outside of the study. If any harm occurs while you are taking part in this research project, you will have all the rights and protection that you normally have as a patient. There are no special compensation arrangements for study participants. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the National Health Service complaints mechanisms (which include professional indemnity insurance) would be available to you.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will answer your questions (eTHoS co-ordinating office 01224 438170). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from the hospital.

In addition to this, you may contact the chairman of the eTHoS Trial Steering Committee through the eTHoS study office. Any complaint you have relating to your participation in the study or any possible harm you might suffer will be addressed.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

Your colorectal surgeon will continue your care and treatment.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

All information that is collected about you will be kept strictly confidential and will be held securely in accordance with the Data Protection Act. Only certain members of the research team will have access to your information, in order that you can be contacted and sent questionnaires. If you participate in the trial, we will notify your GP, unless you prefer that your GP is not informed. Data for all participants in the study, including those who withdraw, will be kept for a minimum of 10 years. As part of the longer term follow-up, the study office will contact you about five years after your surgery to ask how you are keeping and also check your medical notes to find out, for example, if you have had any further haemorrhoid surgery.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

You can withdraw from the study at any time, but you will need to continue attending the colorectal department to have your haemorrhoidal condition monitored, which is part of your standard care. If you become incapacitated during the study, we would withdraw you but all relevant data collected prior to that withdrawal would be retained confidentially.

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

If a new treatment or new information about the two surgical procedures being studied becomes available during the study, you will be made aware of this and you can decide if you would like to continue in the study. You may decide this at any time and your decision will not affect the long-term care. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of the study will be used to standardise surgical procedures for patients with haemorrhoids. These findings will also be published in scientific journals and presented at scientific meetings. The findings will also be made available to patients through patient organisations, health information websites that are open to the public and the media where possible and appropriate.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

The study has been designed by UK colorectal surgeons and researchers. Patients will be recruited at different hospitals throughout the UK. The study is being funded by the UK National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme.

WHO HAS REVIEWED THE STUDY?

This study has been reviewed and approved by the North of Scotland Research Ethics Committee, the Research and Development Department of your local hospital and the study funder (NIHR HTA programme).

THANK YOU

Patients and doctors rely increasingly on the results of clinical studies, such as eTHoS, to make sure they are making the right decisions about treatment. Thank you for taking the time to read this information leaflet, we hope that it has been helpful in enabling you to decide if you would like participate in the eTHoS study.

FURTHER INFORMATION AND CONTACT DETAILS

If you have any questions or would like any more information, please contact:

Central Office contact details: eTHoS Study Office Centre for Healthcare Randomised Trials (CHaRT) Health Services Research Unit University of Aberdeen 3rd Floor, Health Sciences Building Foresterhill Aberdeen AB25 2ZD Telephone: [REDACTED] Email: [REDACTED]
Local contact details:



Patient Information Leaflet post Haemorrhoid Surgery

Each patient is individual to the post operative healing process, but this leaflet aims to provide you with some general information following your haemorrhoid surgery.

PAIN

Do not be alarmed. This is to be expected following your surgery and should decrease over the coming days. You should have been discharged from hospital with painkillers, which you should take regularly as prescribed.

Paracetamol and Ibuprofen can also be taken but please do NOT exceed the stated doses.

Ice packs may also be helpful.

CONSTIPATION

It is very important that you avoid straining when trying to pass a bowel motion so therefore you should have been prescribed a stool softener by the hospital along with your painkillers.

If not, this can be purchased at your local pharmacy / supermarket.

You should try and drink plenty of water, at least two litres in the day and also follow a high fibre diet.

BLEEDING

Seeing blood in your stool is to be expected following surgery and this should gradually decrease as time passes.

If it becomes prolonged or excessive seek medical advice from your GP.

DIFFICULTY IN PASSING URINE

Normally you will not be discharged from hospital until you have passed urine. If you do have difficulty a warm bath may help.

Often the problem is due to swelling and the warm bath may help reduce this. If this persists, again seek medical advice.

INFECTION

Infection is actually very rare following this type of surgery, but if you do feel a bit hot and sweaty or develop a temperature it is advisable to go along to your GP to get checked over.

GENERAL

It is advisable to stay off work for one week at least, perhaps longer, depending on your occupation. Listen to what your body is telling you.

In general the healing process can take two to three weeks but everyone is different.

If you have any concerns or require further guidance please contact your GP practice.

Study Centre No

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[illegible]

* If No, complete ineligible/declined form

Version 1, February 2010



eTHoS INELIGIBLE OR DECLINED FORM

Outline data on patients who are ineligible or who decline participation

Q1 Date of attempted recruitment

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Q2 Year of Birth

Y	Y	Y	Y
---	---	---	---

Q3 Gender

Male

☐

Female

☐

Q4 Diagnosis of haemorrhoids

Grade II ☐

Grade IV ☐

Grade III ☐

Q5 Reasons for non-inclusion - tick all that apply

Previous surgery for haemorrhoids (except Rubber Band Ligation or HALO)

☐

Prior surgical treatment for anal sphincter injury repair, or symptomatic incontinence

☐

Peri-anal sepsis

☐

Known inflammatory bowel disease

☐

Malignant gastrointestinal disease, within the last 5 years

☐

Medically unfit for surgery or for completion of the trial

☐

Unable to complete study questionnaires

☐

Pregnant

☐

Patient does not want to participate in the study:

☐

If provided – the reason the patient does not want to participate:

Other

☐

If other, please state:

Signature: _____

ISRCTN80061723

Version 3.2, January 2013



BASELINE CRF

Study number

--	--	--	--	--

PATIENT DETAILS (Sticker may be used below)

Title: ☐ Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other

--

First name

--

Surname

--

Date of birth

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

NHS number

--	--	--	--	--	--	--	--	--	--	--	--

CHI number

--	--	--	--	--	--	--	--	--	--	--	--

Address (use
hospital label if
available)

--

Contact telephone no.

--	--	--	--	--	--	--	--	--	--	--	--

Mobile no.

--	--	--	--	--	--	--	--	--	--	--	--

CONSULTANT DETAILS

Initials

--	--	--

Surname

--

GP DETAILS

Initials

--	--	--

Surname

--

Address

--

Telephone no

--	--	--	--	--	--	--	--	--	--	--	--

ISRCTN80061723

Version 3.4 May 2013

Date of Baseline Assessment

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

MEDICAL HISTORY**Co-morbidities**Bleeding disorders ☐

Please specify bleeding disorder

--

Systemic medications related to increased risk of bleeding or reduced wound healingAspirin ☐ Warfarin ☐ Clopidogrel ☐ Steroids ☐Immunosuppressants ☐ Other ☐

If Other, please specify

--

CLINICAL DATA

Weight (kgs)

--	--	--

Height (cm)

--	--	--

Has the patient had previous rubber band ligation (RBL)? Yes ☐ No ☐

If Yes, how many episodes?

--

Date of most recent RBL procedure

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Has the patient previously had the HALO procedure? Yes ☐ No ☐

If Yes, how many episodes?

Date of most recent HALO procedure

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

PLANNED date of eTHoS surgery

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Please ensure that the ACTUAL date of surgery is tracked and added to the study database as soon as known, to ensure that follow up questionnaires are triggered correctly

ISRCTN80061723

Version 3.4 May 2013

RANDOMISATION INFORMATION

Telephone Randomisation Service Number

[REDACTED]

Web Address

www.charttrials.abdn.ac.uk/ethos

Inclusion Criteria

- Patients with grade II, III or IV haemorrhoids
- Patients aged 18 years or older
- Written informed consent obtained

Exclusion Criteria

- Previous surgery for haemorrhoids (except RBL or HALO)
- Previous surgery for sphincter injury, or symptomatic incontinence
- Peri-anal sepsis
- Known inflammatory bowel disease
- Malignant gastrointestinal disease, within the last five years
- Medically unfit for surgery or for completion of the trial
- Pregnant women

Confirm patient is eligible

☐

YOU WILL NEED THE RESPONSES TO THE EQ-5D (A1-A5) FROM THE PARTICIPANT BASELINE QUESTIONNAIRE, GENDER AND GRADE OF HAEMORRHOIDS, BEFORE UNDERTAKING THE RANDOMISATION STEP

If possible, prior to randomising a patient, please enter all Baseline CRF and patient questionnaire data via the eTHoS website.

Grade of Haemorrhoids

Grade II ☐Grade III ☐Grade IV ☐

Gender

Male ☐Female ☐

Patient Study Number

--	--	--	--	--

Participant has been randomised to:

SH ☐TH ☐

ISRCTN80061723

Version 3.4 May 2013

eTHoS GP letter and information sheet

<< DATE >>

Dr GPFName GPSName

Patient Study Number:

GPAddress1

GPAddress2

GPAddress3

GPAddress4

GPPostCode

Dear Dr GPSName

eTHoS (either Traditional Haemorrhoidectomy or Stapled)

Patient: Title FName SName Ref No DOB Address1 Address2 Address3 Address4 PostCode

A multicentre UK-wide research study, funded by the National Institute for Health Research Health Technology Assessment Programme is investigating which haemorrhoidal operations are the most clinically and cost-effective for patients with haemorrhoids grade II, III and IV. CentreHosp is one of the participating sites. The trial is needed because there is uncertainty about which type of surgery (stapled haemorrhoidopexy or conventional excisional surgery) is most effective for these patients.

All participants who consent will be followed up and those who are eligible will be randomised to a particular type of surgery. Patients who have grade II (and who have already failed two episodes of rubber band ligation), grade III and IV haemorrhoids are included. We are following up patients after their operations, initially for two years, but hopefully also in the longer term, to identify recurrence rates. More detailed information about the study is provided overleaf.

Your patient has agreed to join the study. He/She has been randomised to one of the surgery groups. We will carry out postal follow up (from our study office in Aberdeen) by asking participants to complete questionnaires before surgery and at approximately 1, 3, 6 weeks and 12, 24 and 60 months after surgery. The questionnaires ask about general health and use of the health service as well as specific information about incontinence and haemorrhoidal symptoms.

We should not normally need to obtain any information from you. However, we would be grateful if you could contact telephone number [REDACTED] or email ethos@abdn.ac.uk if your patient changes address, is too ill to continue taking part, has an adverse event following their haemorrhoid surgery or dies.

If you would like to discuss any aspect of our trial, or require any further details, please do not hesitate to contact the eTHoS Study Office.

Yours sincerely

Jessica Wood
eTHoS Trial Manager

Prof. Angus Watson
eTHoS Chief Investigator

ISRCTN80061723

Version 1.2, February 2015

eTHoS GP letter and information sheet

eTHoS GP INFORMATION SHEET

Title of project

Clinical and cost-effectiveness of two main treatment options for the surgical management of Haemorrhoids grade II, III and IV.

Background

Haemorrhoids are common in all age groups from mid-teens onwards. In England in 2006/2007 approximately 25,000 haemorrhoidal procedures were performed as hospital day-case or inpatient admissions, resulting in significant calls on health service resources. The treatment of haemorrhoidal disease is directed at relieving its related symptoms.

There are two major surgical treatments for haemorrhoids: the conventional excisional haemorrhoidectomy (traditional surgery) and the stapled haemorrhoidopexy. Improved understanding of the pathogenesis of haemorrhoids, increasing belief in the importance of preserving the anal cushions and greater awareness of the high incidence of complications associated with excisional haemorrhoidectomy led to the invention of the stapled haemorrhoidopexy procedure.

Two recent systematic reviews and an HTA monograph compared the two main surgical procedures, revealing that 95% of patients who received stapled surgery had less pain in the immediate post-operative period compared with the traditional surgery but equivalent complication and pain rates occurred with both procedures at day 21. Other potential advantages of stapled over conventional surgery include a reduction of operating time, hospital stay and time to return to work. However, uncertainties around complication rates and recurrence of symptoms and costs precludes its widespread use across the NHS. Over the long term there was a significantly increased rate of residual prolapse requiring re-intervention with stapled haemorrhoidopexy. eTHoS is therefore investigating what is the best surgical treatment for patients who have haemorrhoids grade II (with two episodes of rubber band ligation), III and IV who require surgery.

Brief outline of the study

Ethical approval has been obtained for this study. Written consent has been obtained from participants. Participants will be reviewed in outpatients approximately six weeks after their surgery. Participants are sent postal questionnaires at approximately 1, 3 and 6 weeks and 12 and 24 months after their operation. Our main interest is in the improvement of haemorrhoidal symptoms, as reported by the patients themselves.

Version 1.2, February 2015



DETAILS OF HOSPITAL ADMISSION AND COLORECTAL SURGERY

Study number

Date of admission

 / /

Actual Date of surgery

 / /

Was anticoagulant medication stopped prior to surgery? Yes ☐ No ☐ N/A ☐

If Yes, date medication stopped

 / /

Day case surgery planned?

Yes ☐ No ☐

Initials of colorectal surgeon performing operation:

Initials of supervising consultant surgeon (if applicable)

Grade of operator

Consultant ☐Specialty Doctor (SAS) ☐Surgical Trainee ☐Fellow ☐Other ☐

If Other, please specify

If operation was supervised by a consultant, please tick the box ☐

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Anaesthetist

Is there an anaesthetist present? Yes ☐ No ☐

If Yes, what grade?

Consultant ☐ Specialty Doctor (SAS) ☐ Fellow ☐ Registrar ☐

Other ☐ If Other, please specify

Type of anaesthesia

General ☐ General + LA Block ☐

Local only ☐ Spinal ☐ Other ☐

If Other, please give details

Surgical technique

Please confirm which surgical technique was carried out? (stapled, conventional or other):

Stapled ☐

Stapler used?

Ethicon Stapler ☐

Chex ☐

Covidien ☐

Other (state type of stapler below): ☐

Donut complete? Yes ☐ No ☐

Were skin tags removed? Yes ☐ No ☐

If Yes, how many?

Traditional ☐

Surgical approach?

Open (Milligan Morgan) ☐

Closed (Ferguson) ☐

Other (state type of surgical approach below): ☐

Were pedicles excised? Yes ☐ No ☐

If Yes, how many?

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Other

☐

Please specify below which surgical technique was carried out:

Please confirm if the randomised technique was carried out?

Yes ☐No ☐

If NO, please explain why?

Was the surgical technique changed during the operation?

Yes ☐No ☐

If Yes, which surgical technique was initiated and why was it not completed?

Operation time

Please specify time of: (*using 24 hour clock*)

Entry into operating room

H	H	:	M	M
---	---	---	---	---

Surgery start time (*'knife to skin'*)

H	H	:	M	M
---	---	---	---	---

Surgery stop time (*'procedure finishing'*)

H	H	:	M	M
---	---	---	---	---

Time of leaving operating room

H	H	:	M	M
---	---	---	---	---

Intra-operative complications*

Yes

☐

No

☐

If yes, tick all that apply:

Anaesthetic

☐

Bleeding

☐Need for blood
transfusion☐

Other

☐

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Version 3.2, June 2012

If Other, please give details

Post-operative complications before discharge*

Post-operative bleeding ☐

Pelvic sepsis ☐

Need for blood transfusion ☐

Urinary retention (which
requires catheterisation) ☐

Other ☐

If Other, please give details

**Please complete a Serious Adverse Event form if the patient is admitted to hospital or their hospitalisation admission is prolonged as a result of their haemorrhoid treatment or if the patient dies (any reason). The serious adverse event could be one of those expected, and listed above, or one that is not listed but deemed related to their participation in the eTHoS study.*

Date of discharge

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---



6 WEEKS CRF

Study number

Date of visit

 / /

Participant did not attend visit

☐

Clinical Examination

Examination carried out?

Yes ☐No ☐If yes:

Haemorrhoidal tissue still present?

Yes ☐No ☐

If Yes, please grade

Grade II ☐Grade III ☐Grade IV ☐

Proctoscopy carried out?

Yes ☐No ☐

Clinical findings

Anal fistula

☐

Anal stenosis

☐

Residual anal skin tags

☐

Anal fissure

☐

Other

☐

If Other, please specify

Complications*

Has the patient experienced any of the following complications since discharge? Yes ☐ No ☐

If Yes please tick all that apply:

Requirement for blood transfusion

☐
Urinary retention
(which requires catheterisation)
☐

Wound discharge

☐

Pelvic sepsis

☐
Systemic complication related to haemorrhoids
intervention(s)
☐
Wound not completely healed
(traditional haemorrhoidectomy only)
☐

Has the patient had any other related adverse events not listed above?

Yes ☐No ☐

If Yes, please give details

**Please complete a Serious Adverse Event form if the patient suffers a medically significant serious complication, is admitted to hospital or their hospitalisation admission is prolonged as a result of their*

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Version 3.3, June 2012

haemorrhoid treatment or if the patient dies (any reason). The serious adverse event could be one of those expected, and listed above, or one that is not listed but deemed related to their participation in the eTHoS study.

Further interventions since discharge from surgery

Has the patient had any additional hospital visits or contacts since their haemorrhoid surgery approximately 6 weeks ago?

Yes ☐No ☐

If Yes, what (please tick all that are appropriate and include the date of the intervention)?

Date

Further stapled haemorrhoidopexy

☐

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Further haemorrhoidectomy

☐

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Surgery for complications

☐

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

If surgery for complications, please give details

--	--	--	--	--	--	--	--	--	--

Other colorectal surgery

☐

If other colorectal surgery, please give details

--	--	--	--	--	--	--	--	--	--

Indication for other colorectal surgery

--	--	--	--	--	--	--	--	--	--

Non surgical intervention

☐

If non surgical intervention, please give details

--	--	--	--	--	--	--	--	--	--

Was hospitalisation required for any of the above?

Yes ☐No ☐

If Yes, please provide admission and discharge date(s)

Date of Admission

Date of Discharge

Admission One

D	D	/	M	M	/	Y	Y	Y	Y	D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

Admission Two

D	D	/	M	M	/	Y	Y	Y	Y	D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

Need for further treatment

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Medical treatment

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

Pharmaceutical treatment prescribed? Yes ☐ No ☐

If Yes, please specify GTN Paste ☐ Diltiazem Paste ☐
Other ☐

If Other, please specify

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

If No, go to the next section

Surgical treatment

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

If Yes, please specify below

Rubber band ligation Yes ☐ No ☐

Further stapled haemorrhoidopexy Yes ☐ No ☐

Further excisional haemorrhoidectomy Yes ☐ No ☐

Surgery for complications Yes ☐ No ☐

If surgery for complications, please specify

Other colorectal surgery ☐

If other colorectal surgery, please give details

Indication for surgery

Clinical appointment

Further clinical appointment required? Yes ☐ No ☐

If Yes, please state reason

	WITHDRAWAL/ CHANGE OF STATUS
---	---

To be completed on withdrawal/change of status from study

	Study No										
	<table border="1" style="display: inline-table;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>										
Q1 Date of withdrawal	<table border="1" style="display: inline-table;"> <tr> <td style="width: 20px; height: 20px;">D</td> <td style="width: 20px; height: 20px;">D</td> <td style="width: 10px; height: 20px;">/</td> <td style="width: 20px; height: 20px;">M</td> <td style="width: 20px; height: 20px;">M</td> <td style="width: 10px; height: 20px;">/</td> <td style="width: 20px; height: 20px;">Y</td> <td style="width: 20px; height: 20px;">Y</td> <td style="width: 20px; height: 20px;">Y</td> <td style="width: 20px; height: 20px;">Y</td> </tr> </table>	D	D	/	M	M	/	Y	Y	Y	Y
D	D	/	M	M	/	Y	Y	Y	Y		

Reason for withdrawal

Q2 Participant decided to withdraw? (state reason)

Yes

Q3 Any medical reason for withdrawal? (please state reason)

What is participant withdrawing from?

Q4 Follow-up clinic visits?	Yes	☐	No	☐
Q5 Completing questionnaires?	Yes	☐	No	☐
Q6 Contact by telephone from a member of the eTHoS team?	Yes	☐	No	☐

To Research Nurse/Study Office Staff: only complete if participant explicitly request this:

Q7 Relevant outcome data being collected (via hospital and GP records)?

Yes	☐	No	☐
-----	--------------------------	----	--------------------------



Serious Adverse Event/Death Report Form

To be completed for any Serious Adverse Event (SAE) that is:

- related (resulted from administration of any of the research procedures) and
- expected or unexpected (expected events are listed in section 4.4.1 of the protocol)

ALL deaths must be recorded using this Report Form

eTHoS Study No

--	--	--	--	--

Report Date

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Participant Details:

Participant's Initials

--	--	--

Date of Birth

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Q1. Type of event (cross all appropriate to adverse event – if any boxes are crossed the adverse event is “serious”)

Patient died

Hospitalisation

Prolongation of existing hospitalisation

Persistent or significant disability or incapacity

Life threatening

Considered medically significant by the investigator

Q2. Date of event

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Q3. Brief details of adverse event

--

Q4. Is this an “expected” serious adverse event? Yes ☐ No ☐

Q5. Other relevant history (e.g. diagnostics, allergies, etc)

Q6. Place where adverse event took place/detected

Q7. Details of any intervention required

Assessment of whether the event resulted from administration of any of the research procedures:

Q8. Is it reasonably likely that the adverse event resulted from administration of any of the procedures required by eTHoS?

Yes ☐ No ☐

Q8a. Why?

Q9. Name and position of person making this judgement

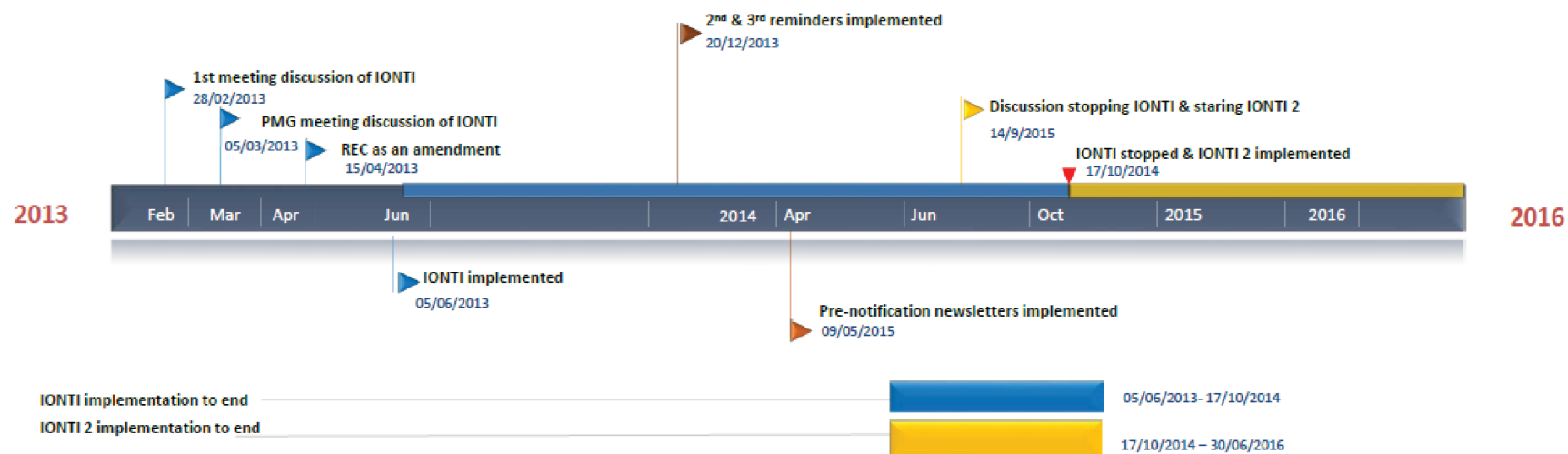
Q9a. Date of assessment

D	D	/	M	M	/	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Appendix 4 'To incentivise or not to incentivise' and 'to incentivise or not to incentivise'-2 appendices

IONTI and IONTI 2 timeline

Time-line



IONTI Covering Letter

eTHoS One, Two year covering letter for IONTI

<< Date >>

<<Title>> <<Name>> << Surname>> eTHoS STUDY No. <<.....>>
 <<Address 1>>
 <<Address 2>>
 <<Address 3>>
 <<Address 4>>
 <<Postcode>>

Dear <<Title>> <<Surname>>

The eTHoS STUDY: either Traditional Haemorrhoidectomy or Stapled Haemorrhoidopexy for Haemorrhoidal Disease

Thank you very much for taking part in the eTHoS Study.

We enclose your {one, two or five year as appropriate} review questionnaire. We are keen to find out how you have been getting on since you first joined the eTHoS study. Please note the page asking for any updates to your contact details. We have enclosed a £5 voucher as a compensation for your time.

Although some of the questions may not seem relevant, we would like you to complete the questionnaire as fully as you can.

Perhaps your treatment didn't work out as planned, or you are now completely back to normal and it all seems like a long time ago. Whatever happened, every person's experience is relevant to the results of the study so we are really interested to hear from you.

If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If you are still in doubt, do please contact the eTHoS Study Office on [REDACTED].

Please return the questionnaire in the reply paid envelope provided (no stamp is required).

We would also like to remind you that you can complete this questionnaire via the eTHoS website at [REDACTED]. Your participant login is: <<loginID>>.

We would like to thank you very much for taking part in the eTHoS Study and for completing the questionnaire as your views and information about your recovery are very important to improving the management of patients having haemorrhoid surgery in the future.

With our very best wishes and thanks for your kind help.

Yours sincerely

Hanne Bruhn
 eTHoS Trial Manager

Version 1.4 31.03.2014

IONTI 2 covering letter

eTHoS One, Two and Five year covering letter

<< Date >>

<<Title>> <<Name>> <<Surname>> eTHoS STUDY No. <<.....>>
 <<Address 1>>
 <<Address 2>>
 <<Address 3>>
 <<Address 4>>
 <<Postcode>>

Dear <<Title>> <<Surname>>

The eTHoS STUDY: either Traditional Haemorrhoidectomy or Stapled Haemorrhoidopexy for Haemorrhoidal Disease

Thank you very much for taking part in the eTHoS Study.

We enclose your (one, two or five year as appropriate) review questionnaire. We are keen to find out how you have been getting on since you first joined the eTHoS study. Please note the page asking for any updates to your contact details.

On return of your completed questionnaire we will send you a token of appreciation (love2shop voucher for £30) for your time spent on completing the questionnaire. If you do not wish to receive this, please tick the box on the front cover of your questionnaire. Although some of the questions may not seem relevant, we would like you to complete the questionnaire as fully as you can.

Perhaps your treatment didn't work out as planned, or you are now completely back to normal and it all seems like a long time ago. Whatever happened, every person's experience is relevant to the results of the study so we are really interested to hear from you.

If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If you are still in doubt, do please contact the eTHoS Study Office on 01224 438170.

Please return the questionnaire in the reply paid envelope provided (no stamp is required).

We would also like to remind you that you can complete this questionnaire via the eTHoS website at [REDACTED]. Your participant login is: <<loginID>>.

We would like to thank you very much for taking part in the eTHoS Study and for completing the questionnaire as your views and information about your recovery are very important to improving the management of patients having haemorrhoid surgery in the future.

With our very best wishes and thanks for your kind help.

Yours sincerely

Jessica Wood
 eTHoS Trial Manager
Enclosures 1, 2 or 5 year eTHoS questionnaire (as appropriate)
Reply paid envelope

Version 1.7, 24.11.2014

IONTI Label



On return of your completed questionnaire we will send you a token of appreciation (a £30 high street shopping voucher) to thank you for the time spent completing the questionnaire. If you do not wish to receive this token of appreciation please tick (✓) this box. ☐

ISRCTN80061723. Version 1.0, Nov 2014

IONTI Compliment Slip



eTHoS Study Office
 Centre for Healthcare Randomised Trials
 Health Services Research Unit
 University of Aberdeen
 3rd Floor, Health Sciences Building
 Foresterhill
 Aberdeen AB25 2ZD

Tel: [REDACTED]
 Fax: [REDACTED]
 Email: [REDACTED]

Please find enclosed a voucher as a token of appreciation for the questionnaire you recently completed and returned to us.

With many thanks

*Please note, depending on your personal circumstances, this voucher may be subject to tax.
 As a recipient of this voucher we are by law required to pass on your details to the HMRC if requested.*

eTHoS is funded by the NHS National Institute for Health Research Evaluation, Trials and Studies
 Coordinating Centre, Health Technology Assessment programme (NETSCC HTA)
 voucher slip_v1_08.09.2014

ISRCTN80061723

Appendix 5 The eTHoS study trial consent form

Participant Study No

--	--	--	--	--

STUDY CONSENT FORM

eTHoS: either Traditional Haemorrhoidectomy or Stapled Haemorrhoidopexy for Haemorrhoidal Disease

Please tick ALL boxes

**By signing this form and ticking each box I agree that I have:**

- been given the Information Sheet about the study (Version 2.1, dated Dec 2011)
- had the opportunity to discuss the study
- received satisfactory answers to questions
- been given enough information about the study

I understand that:

- my participation is voluntary and taking part in the study may not benefit my own health
- I am free to withdraw from the study at any time without having to give a reason
- if I withdraw, this will not affect my medical care or legal rights
- I may be contacted in the future for long term follow-up

I agree that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Aberdeen, from regulatory authorities or from the NHS Board or Trust, where it is relevant to my taking part in this research. Information relevant to the eTHoS study may be collected from my hospital and NHS records, including Office of National Statistics (ONS) and NHS central registers.

--

I agree that relevant data and my contact details will be held confidentially and securely by the study office in Aberdeen, and may be subject to audit and monitoring by regulatory authorities, without breaching data confidentiality

--

I agree that my family doctor (GP) and my hospital consultant may be told that I am taking part in this study

--

I agree to take part in the eTHoS study

--

Your signature (participant)

Your name in block capitals

Date

For office use only

I confirm that I have explained to the person named above, the nature and purpose of the eTHoS study and the procedures involved

Signature

Date

eTHoS Study Office, Centre for Healthcare Randomised Trials (CHaRT),
Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD
Tel: [REDACTED] Fax: [REDACTED] Email: [REDACTED]

Copies: White sent to researchers in Aberdeen; pink to participant, green to site file and yellow to be filed with hospital notes.

ISRCTN80061723

Version 2.2 May 2013

PROJECT SUMMARY

Title of project

Clinical and cost-effectiveness of two main treatment options for the surgical management of Haemorrhoids grade II, III and IV.

Background

Haemorrhoids are common in all age groups from mid-teens onwards. In England in 2006/2007 approximately 25,000 haemorrhoidal procedures were performed as hospital day-case or inpatient admissions, resulting in significant calls on health service resources. The treatment of haemorrhoidal disease is directed at relieving its related symptoms.

There are two major surgical treatments for haemorrhoids: the conventional excisional haemorrhoidectomy (traditional surgery) and the stapled haemorrhoidopexy. Improved understanding of the pathogenesis of haemorrhoids, increasing belief in the importance of preserving the anal cushions and greater awareness of the high incidence of complications associated with excisional haemorrhoidectomy led to the invention of the stapled haemorrhoidopexy.

Two recent systematic reviews and an HTA monograph compared the two main procedures revealing 95% of patients who received stapled surgery had less pain in the immediate post-operative period compared with the traditional surgery but equivalent complication and pain rates occurred with both procedures at day 21. Other potential advantages of stapled over conventional surgery include a reduction of operating time, hospital stay, time to return to work. However, uncertainties around complication rates, recurrence of symptoms and costs, precludes its widespread use across the NHS. Over the long term there was a significant increase rate of residual prolapse requiring re-intervention with stapled haemorrhoidopexy. eTHoS is therefore investigating what is the best surgical treatment for patients who have haemorrhoids grade II (with two episodes of rubber band ligation), III and IV that require surgery.

Brief outline of the study

Ethical approval has been obtained for this study. Written consent has been obtained from participants. Participants will be reviewed in outpatients approximately six weeks after their surgery. Participants are sent postal questionnaires at approximately 1, 3 and 6 weeks and 12 and 24 months after their operation. Our main interest is in the improvement of haemorrhoidal symptoms, as reported by the patients themselves.

Version 1 September 2011

Appendix 6 The eTHoS study amendments

Amendment Number	Substantial/ Non-substantial	Details (docs named in AM approval letters)	Version	Date	Ethical Opinion
AM01	Substantial	Details of Hospital Admission and Colorectal Surgery,	2	July 2010	Favourable
		Baseline CRF	2	July 2010	
		Ineligible and Declined Form	3	August 2010	
		Short Summary	2	August 2010	
		Questionnaire: Baseline Patient Reported Outcome	2	July 2010	
		Protocol	3	August 2010	
		6-Weeks CRF	2	July 2010	
AM02	Substantial	Letter to surgeons	1	December 2010	Favourable
		1 week covering letter	1	December 2010	
		Details of Hospital Admission and Colorectal Surgery	3	December 2010	
		6 Weeks CRF	3	December 2010	
		Baseline CRF	3	December 2010	
		Advertisement	1	December 2010	
		Questionnaire – 1 year	2	December 2010	
		Questionnaire – 2 year	2	December 2010	
		Questionnaire – 5 year	2	December 2010	
		Questionnaire – 6 week	2	December 2010	
		Questionnaire – Baseline	3	December 2010	
		Protocol	4	16 December 2010	
		Questionnaire – Surgeons	1	December 2010	
AM03	Non-substantial	1, 2 and 5 year covering letter	1.1	January 2011	Not required
		1, 2 and 5 year reminder letter	1.1	January 2011	
		6 week covering letter	1.1	January 2011	
		6 week first reminder letter	1.1	January 2011	
		3 week covering letter	1.1	January 2011	
		Participant Cost Questionnaire letter sent at 18 months	1.1	January 2011	

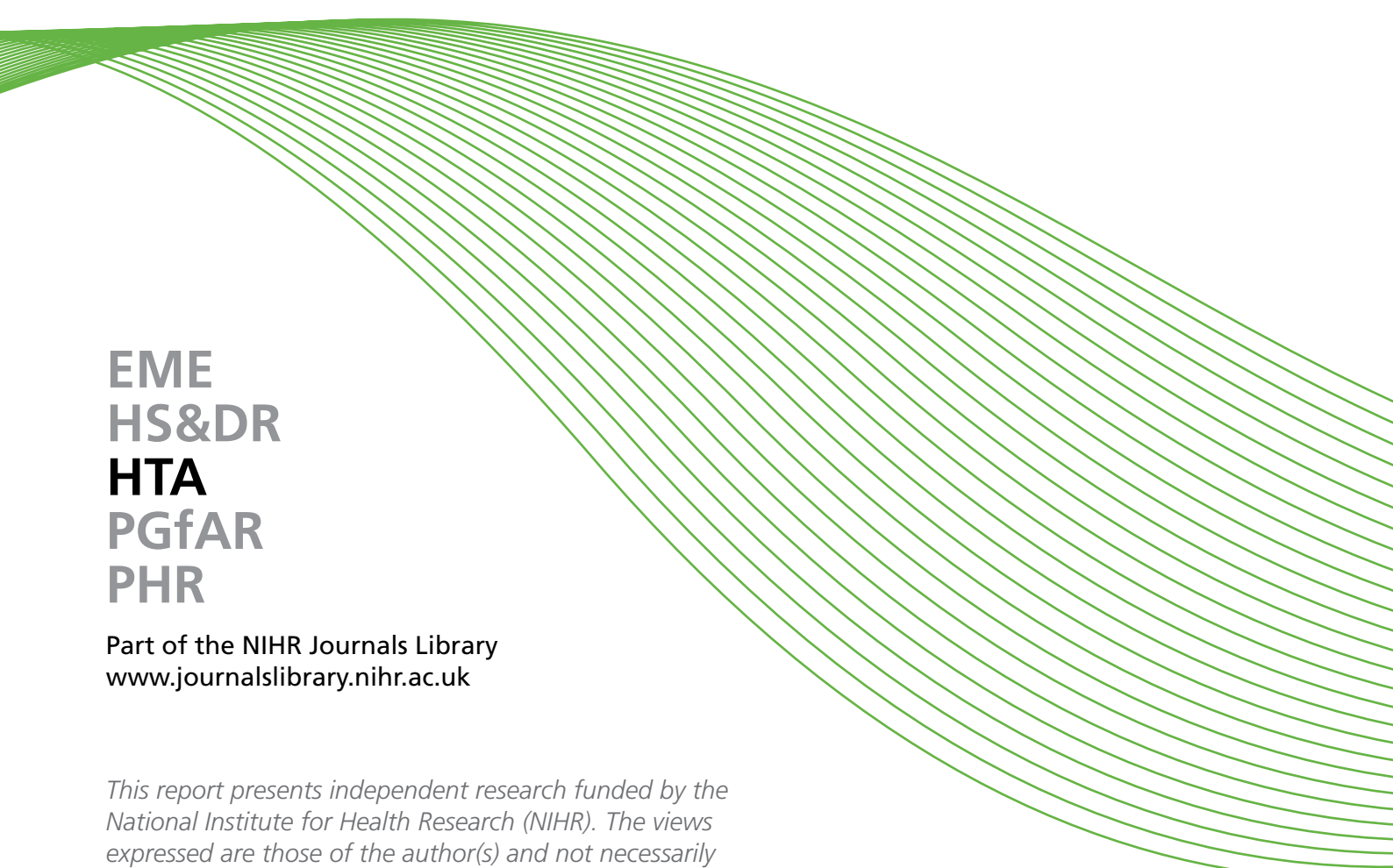
		post haemorrhoid operation			
AM04		Error by REC			
AM05	Non-substantial	Protocol	4.1	24 March 2011	Not required
AM06	Non-substantial	6-week CRF	3.1	May 2011	Not required
		Baseline CRF	3.1	May 2011	
AM07	Substantial	Protocol, v5, Patient Information Leaflet Informed Consent Form Information for back of Consent form Baseline CRF Hospital Admission and Colorectal Surgery CRF Six Weeks CRF One Week Questionnaire Six Week Questionnaire Best Contact first letter Best Contact subsequent letter GP letter	2.1 2.1 1 3.2 3.1 3.2 1.1 2.1 2.1 2.1 1.1	19 January 2012 September 2011 September 2011 January 2012 January 2012 January 2012 January 2012 January 2012 October 2011 October 2011 October 2011	Not approved
AM7-1	Substantial	6 weeks CRF, v 3.2,	3.2	26 March 2012	favourable
		Questionnaire: Participant Costs Questionnaire	1.1	26 March 2012	
		Protocol	5.1	16 March 2012	
AM08		Error in numbering by REC			
AM09	Non-substantial	GP Information Sheet	1.1	October 2011	Not required
		GP Letter	1.1	October 2011	
		Project Summary	1	September 2011	
		Details of Hospital Admission and Colorectal Surgery	3.1	January 2012	

		Questionnaire: 1 Week	1.1	January 2012	
		Questionnaire: 6 Weeks	2.1	January 2012	
		Participant Information Leaflet	2.1	December 2011	
		Best Contact Letter with First Form	1.1	October 2011	
		Baseline CRF	3.2	January 2012	
		Best Contact Subsequent Letter	2.1	October 2011	
		Participant Consent Form	2.1	01 September 2011	
AM10	Non-substantial	Ineligible or declined form	3.1	01 June 2012	Not required
		Serious Adverse Event/Death Report Form	1.1	01 June 2012	
		Details of Hospital admission and colorectal surgery	3.2	01 June 2012	
		6 weeks CRF	3.3	01 June 2012	
		Baseline CRF	3.3	01 June 2012	
		Questionnaire 5 year	2.1	01 June 2012	
		Questionnaire: 6 week	2.2	01 June 2012	
		Questionnaire – Baseline	3.1	01 June 2012	
		Questionnaire 2 Year	2.1	01 June 2012	
		Questionnaire 1 Year	2.1	01 June 2012	
AM11	Non-substantial	1 2 5 year covering letter	1.3	August 2012	Not required
		Questionnaire 1 year	2.2	31 Aug 2012	
		Questionnaire 2 year	2.2	31 Aug 2012	
		Questionnaire 5 year	2.2	31 Aug 2012	
AM12	Substantial	Participant poster (Patient recruitment poster)	1	12 Sep 2012	favourable
AM13	Non-substantial	Questionnaire: Surgeon	1.1	28.9.12	Not required
AM14	Non-substantial	Questionnaire: 2 years	2.3	October 2012	Not required

AM15	Non-substantial	Ineligible or Declined form	3.2	Jan 2013	Not required
AM16	Substantial	Protocol	5.2	25.3.13	favourable
		1 and 2 year covering letter for IONTI	1	25 March 2013	
AM17	Non-substantial	Pt review letter (1 and 2 yr IONTI covering letter)	1.1	29.04.2013	Not required
AM18	Non-substantial	Advertisement (International trials day poster)	5	19.04.2013	Not required
AM19	Substantial	Reminder letter - 1,2 & 5 years	1.3	28.6.13	favourable
		Covering letter - 1,2 & 5 years	1.4	28.6.13	
		Participant Consent form	2.2	May 2013	
		Protocol	5.3	20.05.2013	
		Baseline CRF	3.4	May 2013	
		IONTI - 1 and 2 year covering letter	1.2	28.6.13	
		SAE form	1.2	May 2013	
		Participant agreement to contact	1	4.7.13	
		Participant Keeping in contact Sheet	1	28.6.13	
		Participant Information Sheet: Post Operative Leaflet	1	28.6.13	
AM 20	Non-substantial	6 week covering letter	1.2	Oct 2011	Not required
		6 week first reminder letter	1.2	Oct 2011	
		3 week covering letter	1.2	Oct 2011	
AM 21	Non-substantial	1 week covering letter	1.1	Oct 2011	Not required
		Participant Cost Questionnaire covering letter	1.1	Jan 2011	

AM 22	Substantial	Protocol	5.4	26 Sep 2013	favourable
		Questionnaire : Reminder	1	26 Sep 2013	
		One, Two Year covering letter for IONTI	1.3	26 Sep 2013	
		18 months reminder letter	1	26 Sep 2013	
		1,2,5 Year Reminder 1 and 2 letter	1	26 Sep 2013	
		1,2 and 5 Year covering letter	1.5	26 Sep 2013	
AM 23	Non-substantial	Extension of recruitment from 30 April 2014 to 31 July 2014			Not required
AM 24	Substantial	Newsletter	1a	21 March 2014	favourable
		Newsletter	1b	21 March 2014	
AM 25	Non-substantial	1 and 2 Year covering letter for IONTI	1.4	31 March 2014	Not required
AM 26	Substantial	IONTI-Qual interviews		20 May 2014	Not approved
AM 27	Substantial	IONTI-2		8 Sep 2014	favourable
AM 28		REC numbering error			
AM 29(REC 28)	Non-substantial	GANT chart in Protocol updated to reflect recruitment extension	5.5	17 Dec 2014	Not required
		Addition of opt out sentence to receive voucher for IONTI 2 in 1,2,&5 year cover letter And reminder letter and inclusion of 18 month reminders	1.7,1.6, 1.1		

AM30(REC 29)	Non-substantial	Modified letter for 2Y reminders due to database error (86 reminders were not issued)	1	15 January 2015	Not required
AM30-1 (REC 30)	Non-substantial	Amendment of participant newsletters Amendment of trial manager name on 1week, 3week, 6week, GP letters and participant cost questionnaire covering letters	2a & 2b	5 March 2015	Not required
AM31(REC 32)	Non-substantial	Amendment of participant newsletters	2.1a & 2.1b	4 th September 2015	
AM32 (REC 31)	Substantial	DCE covering letter DCE questionnaire block 1 DCE questionnaire block 2 DCE questionnaire block 3 DCE questionnaire block 4	V1 V1 V1 V1 V1	August 2015	Favourable 15 September 2015
AM33 (REC 34)	Non-substantial	Amendment of participant newsletters	3.a & 3.b	3 December 2015	Not required
AM34 (REC 35)	Non-substantial	Protocol Amendment regarding DCE questionnaire (section 6.3 & 6.4) The number to be sent has been amended from n100 to n400 and the questionnaire is now dispatched at 27 months not 24 months to allow collection of the cost questionnaire.	V5.6	18 February 2016	Not required 23 February 2016
No AM35					
AM36 (REC 36)	Substantial	5 year follow-up questionnaire and covering letters Non-validated questionnaire - Participant Questionnaire eTHos Five year covering letter 5 year reminder 1 and 2 letter	V2.3 V1 V1	June 2016 30 May 2016 30 May 2016	Favourable 21 June 2016
AM37 (REC 37)	Non-substantial	Amendment to 5 year follow-up reminder letter Minor amendment to wording of the 5 year reminder 1 & 2	 V1	 30 June 2016	Not required 30 June 2016

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