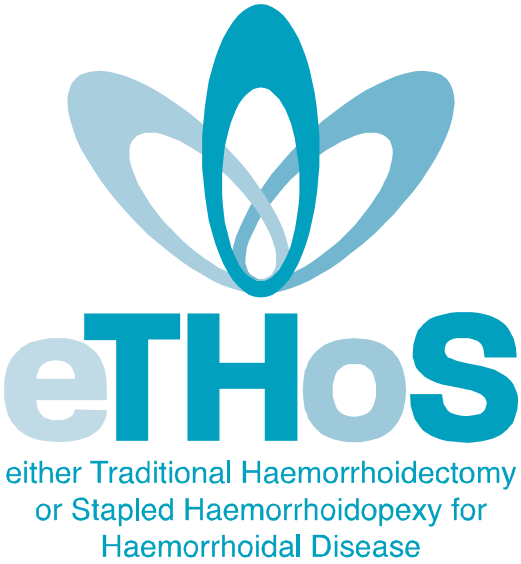

The **eTHoS** STUDY

either **T**raditional **H**aemorrhoidectomy **o**r **S**tapled Haemorrhoidopexy for Haemorrhoidal Disease

A pragmatic multicentre randomised controlled trial comparing stapled haemorrhoidopexy to traditional excisional surgery for haemorrhoidal disease

PROTOCOL

A UK Collaborative Study funded by the NIHR HTA Programme

Version 5.5, 15.09.2014
ISRCTN80061723

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PROTOCOL SUMMARY

QUESTION ADDRESSED	Is stapled haemorrhoidopexy (SH) more effective and cost-effective compared with traditional excisional haemorrhoidectomy (TH)?
CONSIDERED FOR ENTRY	Adults aged 18 years or over for whom surgery for haemorrhoidal disease is recommended. Patients with grade II, III and IV haemorrhoids.
STUDY ENTRY	Consent to RCT will be obtained from eligible patients after written and oral information is provided by local hospital team. All participants complete a questionnaire and undergo assessment before the operation. Patient reported outcomes will subsequently be collected by postal questionnaires sent from the central study office at 1-week, 3-weeks, 6-weeks after surgery, 12, 24 and 60 months after randomisation. Participants will be examined clinically at 6-weeks following their surgery.
INTERVENTIONS	Stapled haemorrhoidopexy: haemorrhoidal prolapse is corrected by excising a ring of tissue above the haemorrhoidal cushions with immediate re-anastomosis of the mucosa using staples. It also reduces blood flow and congestion. Traditional excisional haemorrhoidectomy: there are two main excisional procedures, open (Milligan and Morgan) and closed (Ferguson). Both involve the excision of the haemorrhoidal cushions.
OUTCOME ASSESSMENT	The primary outcome is health-related quality of life derived from EQ-5D measurements at baseline, 1, 3 and 6-weeks, 12, 24 and 60 months. The primary trial economic outcome is incremental cost per QALY at 24 months. Primary economic model outcome is incremental cost per QALY over the lifetime of the patient.
CO-ORDINATION	**Local**: by local colorectal surgeon and local recruitment officers. **Central**: by Study Office in Aberdeen (Telephone 01224 559606). **Overall**: by the Project Management Group, and overseen by the Trial Steering Committee and the Data Monitoring Committee.
FUNDER	The National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme
Start date:	October 2010
Planned finish date:	September 2016
Planned reporting date:	September 2016

GLOSSARY OF ABBREVIATIONS

AUC	Area under the curve
BID	Twice a day
BNF	British National Formulary
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DCE	Discrete Choice Experiment
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
eTHoS	either Traditional Haemorrhoidectomy or Stapled Haemorrhoidopexy
GCP	Good Clinical Practice
GP	General Practitioner
HALO	Haemorrhoidal Artery Ligation Operation
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ISD	Information Statistics Division
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Information Technology
MRC	Medical Research Council, UK
NCT	National Clinical Trial
NHS	National Health Service
NIHR	National Institute Health Research, UK
NRES	National Research Ethics Service
OD	Once a day
PI	Principal Investigator
PEDW	Patient Episode Database Wales
PMG	Project Management Group
PRO	Patient Reported Outcome
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QID	Four times a day
RBL	Rubber Band Ligation
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RO	Recruitment Officer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	Short form health survey 36 question form
SH	Stapled Haemorrhoidopexy
SHSC	Scottish Health Service Costs
TH	Traditional Haemorrhoidectomy
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
VAS	Visual Analogue Score
WTP	Willingness To Pay

eTHoS PERSONNEL

Grant Holders

1 Angus Watson
2 Malcolm Loudon
3 Senior Health Economist
4 David Jayne
5 Ramesh Rajagopal
6 Finlay Curran
7 Steven Brown
8 Jonathan Cook
9 John Norrie
10 Brian Buckley
Health Economist

Trial Steering Committee (TSC):

Independent members

1 Professor Robert Steele (Chair)
2 Mr James Hill
3 Laura Magill

Non Independent members:
(Consists of grant holders)

Observers:

1 Trial Manager
2 Data co-ordinator
3 CHaRT Senior Trials Manager
4 CHaRT Senior IT Manager

Project Management Group (PMG):
Consists of the grant holders, observers of the TSC and other key members of the study team e.g. health economist.

Data Monitoring Committee (DMC) Members:

1 Ajith Siriwardena (Chair)
2 Diane Whitham
3 Angela Crook

Study Office Team:

1 Angus Watson
2 CHaRT Director
3 Trial Manager
4 Jonathan Cook
5 Senior Health Economist
6 Trial Health Economist
7 CHaRT Senior Trials Manager
8 CHaRT Senior IT Manager
9 Data co-ordinator
10 Trial Statistician

Other Information

International Standard Randomised Controlled Trial Number (ISRCTN)	ISRCTN80061723
REC Reference Number	10/S0802/17
NIHR HTA Project Number	08/24/02
CHaRT website:	http://www.charttrials.abdn.ac.uk/ethos

Title of trial: A pragmatic multicentre randomised controlled trial comparing Stapled Haemorrhoidopexy (SH) to Traditional Haemorrhoidectomy (TH).

Acronym: The eTHoS study

This protocol describes a large multicentre UK pragmatic randomised controlled trial (RCT) to establish whether stapled haemorrhoidopexy (surgical) treatment improves clinical effectiveness and cost-effectiveness compared with traditional excisional haemorrhoidectomy.

1. THE REASONS FOR THE TRIAL

1.1 The burden of the problem

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[1]. The treatment of haemorrhoidal disease is directed at relieving its related symptoms. Traditional surgical haemorrhoidectomy (TH) involves excision of the haemorrhoidal cushions and is generally advocated for symptomatic haemorrhoids grade III and IV. This traditional approach, whilst effective, is however associated with severe pain.

Improved understanding of the pathogenesis of haemorrhoids[2], increasing belief in the importance of preserving the anal cushions and greater awareness of the complications associated with excisional haemorrhoidectomy led to the invention of newer surgical procedures including stapled haemorrhoidopexy.

Stapled haemorrhoidopexy (SH) was conceived over 10 years ago and was first described by Longo[3]. Its potential advantages over traditional surgery include a reduction of operating time, hospital stay, time to return to work and postoperative pain[4]. These features would seem to make it attractive to patients and healthcare providers. Nevertheless, uncertainties around complication rates, recurrence of symptoms and costs preclude its widespread use across the NHS.

1.2 The decision to evaluate clinical and cost-effectiveness of the two surgical treatments for haemorrhoids (SH and TH)

There have been multiple randomised controlled trials (RCTs) comparing SH with TH. These RCTs have been analysed in two recent systematic reviews and an HTA monograph[5-7]. The HTA included a review of the clinical effectiveness data from 27 RCTs (n=2279; 1137 SH; 1142 TH). When comparing SH with TH, the authors revealed equivalent complication and pain rates at day 21. However, SH patients had less pain in the immediate post-operative period compared with 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 SH and TH. The economic evaluations of the two interventions reported in the HTA monograph found that TH dominated SH but it should be noted that TH and SH had very similar costs and QALYs. The additional cost of the stapling instrument was largely but not completely offset by savings in operating time and hospital stay. In terms of QALYs, the improvements in quality of life due to lower pain levels in the early post-operative 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 appears to be associated with less pain in the immediate postoperative period, but a higher rate of recurrence in the longer term and increased need for further surgery. These findings are based on data from small trials, all with methodological flaws, and providing limited data on quality of life (or with respect to an economic interpretation, health state utilities) in the early postoperative period. The recent study by Thaha and colleagues reported similar findings[8]. There are, however, a number of potential limiting factors in the applicability of this study. First, the SF-36 data used to measure quality of life did not rule out substantial differences which only a larger trial would be able to detect. Second, the stapling gun has

subsequently undergone refinement (recruitment was completed in 2002). Third, the trial was conducted prior to the stapling technique being well-established in the UK health care system.

Whilst there is a reasonable volume of work on grade III and IV haemorrhoids, there is a paucity of clinical and economic data regarding SH or TH for grade II haemorrhoids. Our group has conducted a RCT comparing rubber band ligation (RBL) with SH for grade II haemorrhoids using both clinical and economic outcomes[9]. This showed a superior clinical effect of SH compared to 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 two 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. However, a larger trial with longer term follow-up is needed to confirm this.

This small trial used similar outcome measures to those being used in eTHoS and had a high return rate over a median follow-up period of 36 months. Internal reproducibility of the symptom score (the Haemorrhoid Symptom Score) was also validated in this trial by re-administration of questionnaires after an appropriate wash-out period[10]. This symptom score measures the presence, frequency and severity of key haemorrhoidal symptoms (prolapse, pain, bleeding, pruritis, seepage and incontinence for flatus or faeces). These symptoms are scored from 0-4 in each domain (except for pain, which scores from 0-2). The Cleveland incontinence score[11] is a standard measure of the degree of disturbance to life caused by incontinence. While it is evident that many patients with haemorrhoids have mild disturbance mainly related to flatus, the main utility is in detecting any problems related to sphincter injury as a result of surgery.

There is therefore a need for an adequately powered, high quality, multicentre RCT comparing the clinical and cost-effectiveness of SH compared with TH. Patient reported health status will be observed over the trial period as well as symptoms related to haemorrhoids, general health and complications from either procedure.

1.3 The questions which this study will address

The aim of eTHoS is to assess for people with haemorrhoids (grade II, III and IV), whether stapled haemorrhoidopexy (SH) is more effective and cost-effective compared with traditional excisional haemorrhoidectomy (TH).

The primary objective is to compare patient reported overall health related quality of life (measured using the EQ-5D) over a period of 24 months.

The secondary objectives are to compare sub-domains of health (SF-36 scores, pain and symptoms), disease recurrence, complication rates, and direct and indirect costs to the NHS, and cost-effectiveness (measured in terms of incremental cost per QALY, where QALYs are derived from responses to the EQ-5D).

eTHoS is a pragmatic, multicentre, superiority, parallel group trial comparing SH and TH.

2. TRIAL RECRUITMENT AND ALLOCATION

In order to run the study according to the protocol each hospital centre participating in the eTHoS study will require at least two members of staff to occupy two key research roles. One research role is that of a (co-investigating) colorectal consultant; the other will be a local Recruitment Officer (RO) e.g. a nurse or junior doctor. In exceptional circumstances the colorectal consultant may perform both roles. At each centre there may be more than one colorectal consultant (co-investigator) who will be fully eTHoS trained and actively screening potential patients (for eligibility) and subsequent recruitment onto the trial. At each centre one of these consultants will assume the leading role of local lead colorectal surgeon for eTHoS. The RO will work with all of the named

eTHoS study colorectal surgeons and, with the lead, will administer the trial in accordance with the protocol.

2.1 People considered for trial entry

Inclusion criteria:
- Patients with circumferential haemorrhoids grade II, grade III and IV
- Patients aged 18 years or older
- Written informed consent obtained

Exclusion criteria:
- Previous surgery for haemorrhoids (traditional or stapled) (except Rubber Band Ligation (RBL) or Haemorrhoidal Artery Ligation Operation (HALO))
- Previous surgical treatment for anal sphincter injury repair, 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

2.2 Recruitment and administration of follow-up procedure for eTHoS

Participant surgeons from each collaborating colorectal surgical unit will identify patients referred to hospital for surgical treatment. Those meeting the eligibility criteria will be invited to enter the trial. Patients who accept the invitation to join the trial will be randomly assigned to be treated by either SH or TH. Outcome assessment will be at 1-week, 3-weeks and 6-weeks after surgery and 12 months, 24 months and (subject to securing further funding) 60 months after randomisation. If response to longer term follow-up (1 year or later) is lower than anticipated, approaches to address this will be considered, and REC approval sought if appropriate.

2.2.1 Recruitment Procedure

Local procedures at the participating hospitals are different and the timing and mode of approach to patients and the consent process will vary to accommodate both the variability at the sites and the needs of the patients.

Eligible patients will be identified in the clinic setting by the colorectal surgeon or a suitably qualified trained member of the local clinical team and noted in an eTHoS log book. The colorectal surgeon will inform the patient during this initial consultation about the different treatments available for their condition as well as giving information about the eTHoS study. As is normal clinical practice, the colorectal surgeon will explain the risks and benefits of all the treatment options.

The colorectal surgeon, or local trained clinical team member, will give each potential participant the Patient Information Sheet. This explains the rationale behind the eTHoS study, as well as what taking part encompasses. The colorectal surgeon, or locally trained clinical team member, will then be on hand to answer any questions/discuss the study with the potential participant during/ immediately after this consultation appointment or at home. Patients will be encouraged to take home and re-read in detail the Patient Information Sheet (already given) during this time. If the patient agrees to be contacted at home he/she may receive a telephone call from a local study team member to discuss the trial. Patients who decide to participate following telephone counselling can either send their completed documents (consent form and baseline questionnaire) through the post to the local study team at their treating hospital or bring it with them if/when they are returning to hospital for pre-op assessment or at the time of the operation.

Patients who are able to make a decision to join the study whilst they are at the clinic will be provided with the eTHoS participant baseline questionnaire that comprises the EQ-5D, SF-36, Cleveland Incontinence Score and Haemorrhoids Symptom Score. Contact details of both the local and central team are provided on the Patient Information Sheet. Patients who require more time to

consider participation in the study will be encouraged to contact either the local or central team if they have any queries that they would like clarification on before they return to hospital. The potential participant will then be re-approached by a local clinical team member prior to surgery. If a patient does not return for pre-assessment (e.g. if they live remotely or due to local site procedures), then the patient can return their signed consent form by post to their recruiting site. The form will be counter-signed on receipt by the local clinical team member. The patient will be advised to contact the site staff by telephone for further clarification or information if needed.

These arrangements will be individualised for each centre. Following full written consent and baseline data completion, patients will be randomised, as near to their surgery as possible, to one of the two study groups in equal proportion using the randomisation application at the trial office in CHaRT (see 2.3). Patients who return their signed consent forms by post will then complete the baseline questionnaire prior to surgery, to enable randomisation to take place.

The outcome of the recruitment consultation(s) with each potential eTHoS participant will be fully documented in an eTHoS log book. For those who consent to participate, a copy of their signed consent form will be filed in the patient's hospital record. In addition, a copy will be given to the participant, a copy will be held in the investigator's site file and the original will be retained by the research office in Aberdeen.

For those patients who do not consent to participate, an 'Ineligible/Declined' form will be completed by a local clinical team member, detailing non personal data, including the reason(s) for the participant declining, or the ineligibility criterion. These data will be recorded on the study database.

2.2.2 Follow-up procedure

Participants will be followed up as described in section 6 of the protocol and the schedule for assessment and data collection (see Figure 1, Section 3). The eTHoS patient follow-up will consist of a visit to the hospital, approximately 6 weeks after surgery (range allowed 4-8 weeks), for a clinical consultation and assessment. At randomisation, both the participant and the surgeon will be aware of the treatment randomisation group. Data collected at all participant visits (including the initial consultation/eligibility visit) will be recorded in the first instance on paper case report forms (CRFs) then entered onto the trial database via a secure web portal.

The trial office in CHaRT, Aberdeen, will coordinate follow-up and data collection in collaboration with the UK centres. The study web portal will be the fulcrum of all trial documentation and facilitate communication between study personnel. All participant reported outcomes (PROs) (apart from baseline) will be collected by postal questionnaires administered from CHaRT.

2.2.3 Additional clinic or hospital visits

Data on any additional hospital visits will be recorded on the CRF completed when participants return for the 6-week clinical follow-up, or in the patient reported outcomes.

2.2.4 Participant withdrawal

Participants will remain on the trial unless they choose to withdraw consent or if the PI, CI or trial office feel it is no longer appropriate for the participant to continue (i.e. participant becomes unable to complete the trial documentation). The reason for the participant being withdrawn from the trial will be recorded on the 'withdrawal/change of status' form and if the participant is still willing to complete follow up questionnaires and/or to have relevant outcome data collected from NHS records then the follow up process will continue.

2.2.5 Training

Training and support will be given in a standardised format to both the colorectal surgeons and the ROs. Training, by a member of the study team, will focus on the eTHoS trial flowchart and the protocol. Training in physical baseline and follow-up measurements will also be given to the ROs if required. The colorectal surgeons and the ROs will use standard study instruction manuals and documentation, which will be provided by the study office for reference and support throughout. The study office will also be the first point of contact for the colorectal surgeons and the ROs in

case of problems, concerns, adverse effects or the need for advice. Recruitment Officer training days will also be held in a variety of UK locations.

2.2.6 Specific eTHoS roles and responsibilities:

It is envisaged that the duties of both the principal local investigator and co-investigating colorectal surgeons and the ROs will be managed between them according to capacity and in accordance with the eTHoS protocol. Main responsibilities/duties are outlined in section 9.1.

2.3 Randomisation and allocation

Participants will be randomised to one of the two study groups in equal proportion using a randomisation application at CHaRT in the Health Services Research Unit, University of Aberdeen. This randomisation application will be available 24 hours a day, 7 days a week and has both an Interactive Voice Response (IVR) telephone and web based interface. Randomisation will take place as near to the time of surgery as possible.

The minimisation algorithm[12] will use centre, grade of haemorrhoidal disease (II, III or IV), baseline EQ-5D score and gender.

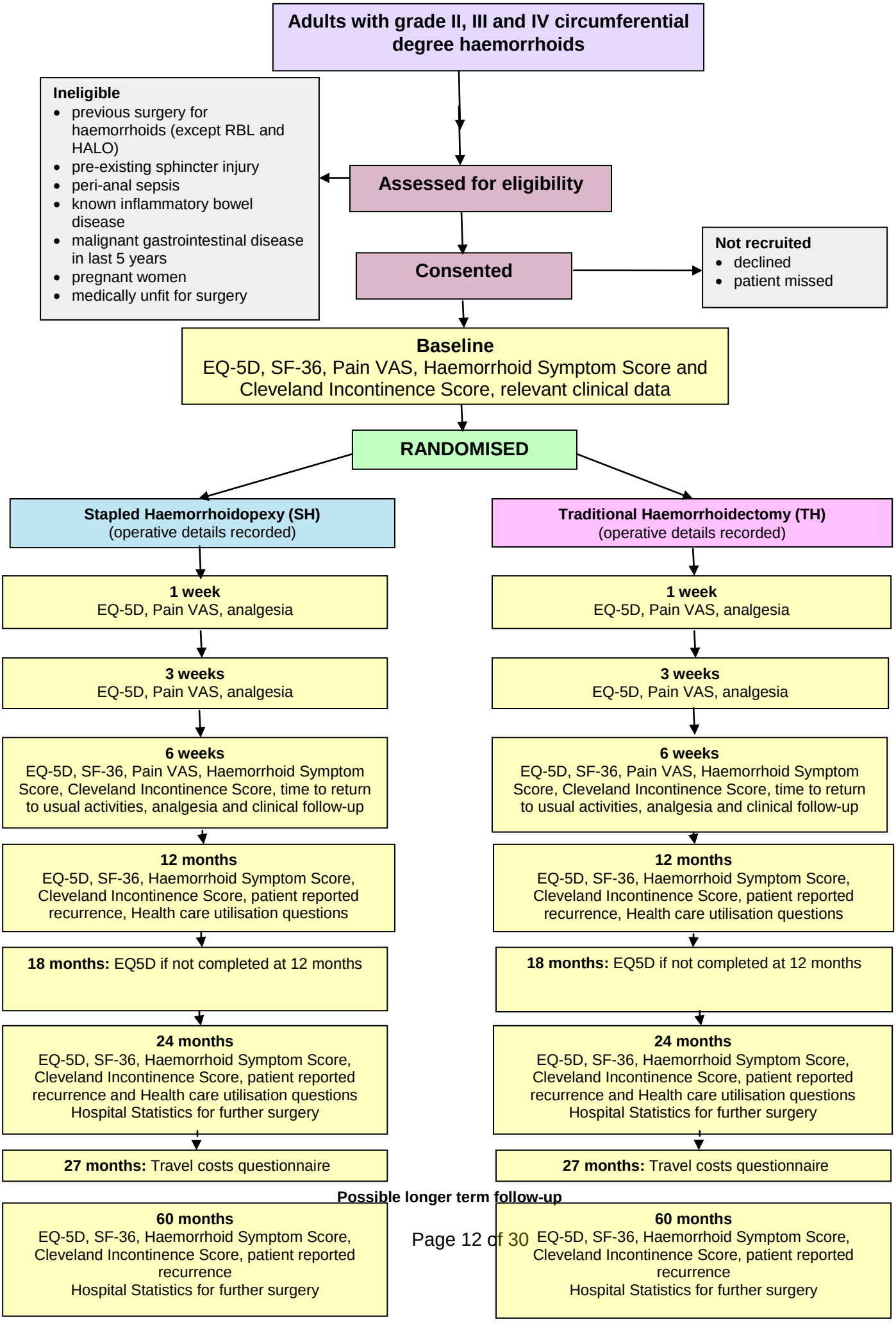
3. TRIAL INTERVENTIONS

Eligible and consented participants will be placed on the appropriate waiting list by the treating colorectal surgeon or his/her designated team member. Participants will receive the allocated intervention, either SH or TH. Each centre's participating surgeons must have undergone appropriate recognised training for both stapled and traditional haemorrhoid surgery. Ideally this will have included attendance at a 'master class'. Surgery can be performed by surgeons in training; either independently, if signed off by their supervising consultant, or under the direct supervision of their consultant. Pre- and post-operative care is to follow the respective surgeon's and centres standard policies.

Baseline data and follow-up measurements are recorded throughout the study on the eTHoS Case Report Forms (CRF).

Refer to Figure 1, Study Flow Chart.

Figure 1: Study Flow Chart



3.1 Stapled Haemorrhoidopexy

The patient will undergo stapled haemorrhoidopexy. Each centre must house experienced surgeons who have undergone appropriate surgical training to perform stapled haemorrhoidopexy (SH).

- Stapled Haemorrhoidopexy (SH) aims to correct haemorrhoidal prolapse by excising a ring or "donut" of tissue above the haemorrhoidal cushions with immediate re-anastomosis of the mucosa using staples. A secondary effect may be to reduce blood flow and therefore congestion. Fibrosis develops at the staple line maintaining the haemorrhoids in their new position. The main stapling gun in use in the United Kingdom is the PPH03 (Ethicon Endosurgery, Johnson & Johnson), which is used by the majority of colon and rectum surgeons. Covidien have recently introduced a dedicated stapling instrument for haemorrhoidal surgery which is similar in design to the stapler provided by Ethicon Endosurgery. Chex Healthcare are newer to this market and have produced a stapler which is very similar to the one made by Johnson and Johnson. There are some key differences - it is around 40% cheaper and has a design which may make it easier to use in male patients. SH is conducted using a stapling gun. Reflecting the pragmatic nature of the trial, surgeons will be able to use the gun which they would normally use in practice.

3.2 Traditional Excisional Haemorrhoidectomy

There are two main excisional procedures currently carried out: open (Milligan and Morgan) and closed (Ferguson). Both have the intention of excising the haemorrhoidal cushions and are traditionally associated with severe postoperative pain. The apparent efficacy of the procedures may be in part due to reluctance of patients to seek further treatment in the light of previous experience. Participating surgeons are required to have undergone appropriate surgical training and be competent to perform traditional excisional haemorrhoidectomy (TH).

4. SUBSEQUENT ARRANGEMENTS

4.1 Notification of GPs

General Practitioners (GP) will be notified by letter, which includes a GP eTHoS information sheet, that their patient has been randomised to the eTHoS study. GPs are asked to phone the Study Office if the participant moves, becomes too ill to continue with the study, dies, or any other notifiable event/possible adverse event occurs. Alternatively, staff at the Study Office may contact the GP.

4.2 Flagging on central medical databases

Consent will be sought from all participants recruited to the RCT to be flagged for notification of haemorrhoidal recurrence. To evaluate long term safety, the participants will be flagged for further haemorrhoidal surgery through Hospital Episode Statistics (HES) in England , Patient Database Wales (PEDW) in Wales and Information Services Division (ISD) data in Scotland, when all participants have reached 12 & 60 months.

4.3 Safety

We will report serious adverse events in accordance with the guidance from the National Research Ethics Service (NRES) which is a subdivision of the National Patient Safety Agency.

4.3.1 Possible expected occurrences

In this study the following occurrences are potentially expected:

Possible (expected) intraoperative occurrences associated with the intervention include anaesthetic related problems, intra-operative instrument failure, damage to adjacent organs and bleeding. Possible (expected) occurrences associated with either type of surgery occurring at any time during the trial includes haemorrhage, requirement for blood transfusion, anal stenosis, anal fissure, pain,

urinary retention, residual anal skin tags, anal fistula, prolapse, difficult defecation, faecal urgency, wound discharge, pelvic sepsis, systemic complications and pruritis.

Details of any of the occurrences listed above will be recorded on the case report forms and participant completed questionnaires and reported to the Data Monitoring Committee (DMC).

4.3.2 Procedure for reporting untoward and related SAEs in this study

A Serious Adverse Event (SAE) in the eTHoS trial is defined as an event occurring to a research participant that is:

- related (resulted from administration of any of the research procedures) and
- expected (see Section 4.4.1) or unexpected (i.e. the type of event that is not listed above in Section 4.4.1 as an expected serious occurrence) that causes death, is life threatening, requires hospitalisation, results in significant incapacity/disability or is otherwise considered medically significant by the investigators.

All SAEs will be recorded on the Serious Adverse Event Report form. In addition, SAE forms will record all deaths due to any cause during the course of the study.

4.3.3 Reporting responsibilities of the Chief Investigator

When the web-based Serious Adverse Event form is completed detailing any possible related and unexpected SAEs, the Chief Investigator (CI) will be notified automatically. If, in the opinion of the local investigator and CI, the event is confirmed as being related and unexpected the CI will submit a report to the main REC and the study sponsors within 15 days of the CI becoming aware of it or within 7 days if it is a death (related to the study).

5. MEASURES OF OUTCOME

The study has a patient-centred and an economic primary outcome, and multiple secondary patient-reported, clinical and economic outcomes.

Primary

Patient-centred: Quality of life profile over follow-up period (area under the curve derived from EQ-5D measurements at baseline, 1-week, 3-weeks, 6-weeks, 12 months, EQ-5D only at 18 months if not completed at 12 months, 24 months and 60 months.

Trial economic: Incremental cost per quality adjusted life year (QALY) gained with QALYs based on the responses to the EQ-5D at 24 months.

Economic model outcome: Incremental cost per QALY over the lifetime of the participant.

Secondary

Patient-reported:

- Generic health profile measured by SF-36 and EQ-5D
- Visual analogue scale (VAS) pain score
- Cleveland Incontinence Score
- Haemorrhoid Symptom Score
- Post operative analgesia consumption
- Recurrence of haemorrhoids
- Tenesmus

Clinical:

Peri and post operative complications including:

- haemorrhage

- requirement for blood transfusion
- anal stenosis
- anal fissure
- urinary retention (which requires catheterisation)
- residual anal skin tags
- difficult defecation
- wound discharge
- pelvic sepsis
- pruritis

***Economic*:**
Costs will be based on resource use data

- Costs to the NHS and patients at two years
    - time to recovery
    - 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
        - visits to GP
        - visits to practice nurse
        - visits to colorectal surgeon

- Estimated lifetime cost to NHS and patient

- QALYs estimated from the EQ-5D at 24 months

- QALYs estimated over the patient's lifetime

- Cost-effectiveness analysis (incremental cost per case of stapled haemorrhoidopexy and traditional haemorrhoidectomy excision avoided).

6. DATA COLLECTION AND PROCESSING

Participants will be recruited up to 43 months. Follow-up will consist of clinical follow-up at 6 weeks and postal questionnaires at 1, 3, and 6 weeks and 12 (and 18 months if EQ-5D not completed at 12 months), 24 and 60 months (see study schedule in 6.4), with the main outcome assessment planned once 24 months (from the date of randomisation) follow-up is complete.

6.1 Measuring outcomes

In this study the colorectal surgeon and the participant will know which intervention the participant has received. Clinical outcomes will be collected by the ROs and the colorectal surgeons.

Patient reported outcomes

At baseline, (recruitment) participants will complete the PRO questionnaires. In addition at 1, 3 and 6-weeks, 12 (EQ-5D only at 18 months if not completed at 12 months), 24 and 60 months participants will complete the eTHoS PRO questionnaires. These will be distributed by post and completed by the participant. Participants will be given the option to complete the 1, 3, 6 week and 1 (EQ-5D only at 18 months if not completed at 12 months), 2 and 5 year participant reported outcome questionnaires on a secure participant portal within the eTHoS website. Participants will be provided with a log-in to access the portal. In the event that these postal questionnaires are not returned, for the 1 and 3 week questionnaires, participants will be telephoned to obtain the missing data. A postal reminder will be sent if there is no response to the 6 weeks, 12, 24 and 60 months questionnaires. If they are not returned, a second short (EQ5D only) reminder will be sent.

6.2 Health Care Utilisation

NHS costs for health services use in both secondary and primary care by the UK trial participants will be collected.

At 12, 24 and 60 months after randomisation, participants will provide information about their use of health services (via the health care utilisation questions within the eTHoS patient reported outcome instrument**.** A postal questionnaire survey of all participants will be used to ascribe costs to typical episodes of health service use (the Participant Travel Cost Questionnaire) sent approximately 27 months after randomisation. The underlying aim is to keep economic data collection as parsimonious as possible to minimise the burden on the participants and the effect on response rates.

6.3 Patient Preference (Baseline and Discrete Choice Experiment)

Burch and colleagues[7] found that the two treatments differed in terms of short-term outcomes (earlier return to usual activities, pain) and differed in terms of the risk of recurrence. Quality of life measurement (and QALYs based upon them) may not fully represent patients' preferences for treatments and their associated outcomes. Given this, global patient preference will be elicited at baseline using a single 5-point Likert scale response to a hypothetical example. Furthermore, a discrete choice experiment (DCE) to allow an in-depth elicitation of the individual strength of preference for the different treatments during the follow-up period will be conducted. The choice of attributes will relate to the trial outcome measures and reflect advice from members of the trial team, as well as evidence from the appropriate literature. One further attribute of the DCE will be patient cost, which will allow willingness to pay (WTP) to be estimated. In particular, willingness to pay for specific attributes of treatment will be assessed. Estimating willingness to pay from the DCE will enable these estimates to be combined into the broader economic evaluation. The DCE will also include an additional surgical intervention, Haemorrhoidal Artery Ligation (HAL) to take into account all the treatment options available to patients with haemorrhoids.

The DCE will describe the intervention in terms of a number of characteristics (attributes) e.g. time in short-term pain and risk of recurrence. The extent to which an individual values an intervention will depend upon the levels of these attributes.[13,14] The DCE technique involves presenting choices to individuals that imply a trade-off in terms of the levels of the attributes. To define the attributes and levels for the DCE, a literature review will be conducted as well as taking expert advice on potential attributes from members of the research team. Once the attributes and levels are defined, experimental design techniques will be used to reduce the number of possible choice sets to a manageable size, whilst still being able to estimate utility scores. In addition to the choices derived from the experimental design, two choice sets will be added to test the internal consistency of responses. These will be dominant (better) choices for one option and respondents would be expected to choose them.

The questionnaire will be piloted amongst a small sample (members of the research group and Health Services Research Unit, Aberdeen) to refine all practical aspects of the survey and to ensure that respondents are making trade-offs between the attributes. Once the pilot is complete and the questionnaire refined, a proportion of trial participants (n=100) will be sent the DCE questionnaire. The questionnaire will then be sent to an on-line survey panel of non-trial participants. Generalised linear (e.g. logistic) regression models will be used to analyse the response data. The decision on which statistical model to use to analyse the data is an empirical one and will depend to a certain extent on the final data collected.

6.4 eTHoS schedule for Physical Assessment/Data Collection

	Baseline	Surgical form	1-week	3-weeks	6-weeks	12 months	18 months	24 months	27 months	60 months
Clinical Status CRF or data	○				○					
Surgical details		○								
Patient preference	○									
6 weeks clinical follow up					○					
EQ-5D	○		●∞	●∞	●∞	●∞	●∞	●∞		●∞
SF-36	○				●∞	●∞		●∞		●∞
Pain VAS			●∞	●∞	●∞					
Haemorrhoid Symptom Score	○				●∞	●∞		●∞		●∞
Cleveland Incontinence Score	○				●∞	●∞		●∞		●∞
Health care Utilisation questions						●∞		●∞		●∞
Travel costs questionnaire									●∞	
Recurrence						●∞x		●∞		●∞x
Analgesia question			●∞	●∞	●∞					
DCE								∞ ●		
Hospital Statistics for further surgery						●∞x				●∞x

○ Clinic ● Postal **x** HES, PEDW and ISD ∞Web based

6.5 Data processing

Clinical data will be collected at the individual hospital centres using, where necessary, hospital based records and hardcopy CRF forms. These clinical data will then be input into the eTHoS database by local researchers using an electronic web-based data capture system (in addition relevant clinical data will be collected from routine data sources (HES, PEDW & ISD). Extensive range and consistency checks will enhance the quality of the data. Staff in the Study Office will provide periodic data queries to local research staff to ensure that the data are as complete and accurate as possible.

7 ANALYSIS PLANS

7.1 Ground rules for the statistical analysis

Study analyses will follow a statistical analysis plan agreed in advance by the Trial Steering Committee. The main statistical analyses will be based on all participants as randomised, irrespective of subsequent compliance with the treatment allocation.

The primary outcome, area under the quality of life curve (measured by EQ-5D), will be generated for each participant using the trapezoidal rule. Missing EQ-5D data will be estimated using a multiple imputation approach which makes use of partial outcome data[15]. Sensitivity analyses will be conducted to assess the robustness of the treatment effect estimate to these approaches. The primary outcome measure will be analysed using linear regression with adjustment for the minimisation variables. Secondary outcomes will be analysed using generalised linear models with adjustment for minimisation and baseline variables as appropriate. Statistical significance will be at the 2-sided 5% level with corresponding confidence intervals derived. Subgroup analyses will explore the possible treatment effect modification of clinically important factors (grade and gender), through the use of treatment by factor interaction, all using a stricter 2-sided 1% level of statistical significance.

An independent Data Monitoring Committee (DMC) will meet early in the course of the trial to agree its terms of reference and will review confidential interim analyses of accumulating data.

7.2 Timing and frequency of analyses

A single principal analysis is anticipated once the final participant has reached the 24 months time point. The DMC will determine the frequency of confidential interim analyses. The potential for analysing longer-term follow-up data (post 24 months) will be assessed once the principal analysis has been carried out.

7.3 Planned subgroup analyses

Subgroup analyses are planned to investigate the influence of haemorrhoidal grade and gender.

7.4 Economic analysis

7.4.1 Costs of management of haemorrhoids for eTHoS participants

Participant costs will comprise 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 will be 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 unit cost of making a return journey to each type of health care provider (from the Participant Unit Cost Questionnaire).
- The cost of participant time will be estimated in a similar manner. The participant will be asked, in the Participant Unit Cost Questionnaire, how long they spent travelling to and attending their last visit to each type of health care provider. Participants will also be asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health care provider. These data will be presented in their natural units, e.g. hours, and also cost estimates using standard economic conventions, e.g. the Department of Transport estimates for the value of leisure time. These unit time costs, measured in terms of their natural and monetary terms, will then be combined with estimates of number of health care contacts derived from the health care utilisation questions.

7.4.2 Costs of intervention

The costs of the surgical interventions will be recorded on a per patient basis. The resources used to provide surgery will be calculated by consulting with relevant staff (surgeons, theatre nurses, business managers) and members of the trial team to elicit information on:

- reusable equipment,
- frequency of use of that equipment,
- consumables used during surgery,
- staff mix of the surgical team and
- overheads costs for specific time periods.

In addition to this, the operative details will be collected on the CRFs and will provide estimates of the grade of operator, assistant and anesthetist, as well as relevant procedure times.

Unit costs for these resources will be based on nationally available data and study-specific estimates. Longer term estimates of resource use and cost will be derived from trial estimates and the literature.

Length of stay information will be elicited for each patient through the case report forms by collecting the date of admission and discharge. Unit costs for each level of care will be initially obtained from the Scottish Health Service Costs (SHSC)[17] for the primary analysis and NHS National Reference Costs in a secondary analysis. These sources will not have a cost per day for all hospital services, therefore some calculations will be needed to determine the 'cost per day' for each level of care.

7.4.3 Costs of subsequent care

The number of outpatient visits per patient for each relevant specialty will be obtained from the case report forms. Unit costs for outpatient visits will initially be obtained from the SHSC[17] for the primary analysis and National Reference Costs in the sensitivity analysis.[18]

The number of General Practice contacts e.g. GP office or home visits or phone consultations will be obtained from the Health Service Utilisation Questionnaire. Unit costs for GP visits will be obtained from the Personal Social Services Research Unit (PSSRU) unit costs of community care[18]. For each patient the number of visits will be multiplied by the appropriate unit cost. These costs will be summed to produce a total cost per patient. When a cost for each patient has been estimated, a mean cost for each intervention group will be calculated.

Any reoperations or new surgical interventions will be identified from the case report forms and costed using data from routine data sources[17,18] or operation costs previously estimated for the study. Any duration of any relevant admissions during the follow-up period will be estimated from the case report forms and costed using the methods described above.

7.4.4 Cost effectiveness

As part of this study an economic evaluation will be conducted. It will be based on both a modelling exercise and a "within trial" analysis. Either an existing, or *de novo,* economic model will be used to assess the relative cost-effectiveness (assessed in terms of incremental cost per QALY) and net benefits of SH and TH. A model was developed as part of a recent HTA funded project and we have negotiated access to that model[7]. Our group has also developed a model to compare the cost-effectiveness of SH and RBL for grade II haemorrhoids. We will critique these models and use, or adapt them, to address our study question. If necessary we will use the lessons learnt from these models to develop a new model that better addresses the research question. The data from the trial will be the main source of data for the modelling but further data with which to model outcomes beyond a 24 month follow-up will be systematically derived from the literature and other existing data sources following guidance for best practice[16].

Data collection from the trial will focus on estimating the use of secondary and primary care resource use and on health state valuations obtained from EQ-5D. Resource use and patient costs will be obtained from participant completed questionnaires at 12 and 24 months. Unit cost will be based on nationally available data and study-specific estimates. Longer term estimates of resource use and cost will be derived from trial estimates and a structured review of the literature. QALYs will be estimated from the responses to the EQ-5D valued using the UK population tariffs.

The results of the economic model will be supplemented by a within trial analysis. This analysis will use the estimates of costs and QALYs estimated for each trial participant to calculate the incremental cost-effectiveness ratios for the 24 month follow-up and where appropriate the analysis will mirror the statistical analysis described in section 7.1 above (e.g. incremental costs and QALYs will be adjusted for the minimisation variables using regression techniques). To facilitate interpretation of the trial results, the within trial economic analysis will also be presented in the form of a balance sheet where differences in terms of benefits and costs of the two trial interventions are presented in their natural or clinical units.

The perspective of the model and within trial analyses will be the patient and the UK NHS. The results of the analyses will be presented as point estimates of mean incremental costs, effects and incremental cost per QALY. Sensitivity analysis will be applied to the model in order to assess robustness of the results to realistic variations in the levels of the underlying data and also alternative assumptions, e.g. QALYs derived from the SF-36. This will be accomplished using probabilistic and deterministic sensitivity analyses to address parameter and other forms of uncertainty. Similarly, for the within trial analysis, techniques such as bootstrapping will be used alongside deterministic sensitivity analyses to address uncertainty. In both the model and the within trial analyses the cost per QALY data will be presented in terms of cost-effectiveness acceptability curves (CEACs).

7.4.4.1 DCE Analysis

The results of the DCE will be combined with the clinical outcomes estimated from the trial or model to provide an estimate of the mean WTP for each intervention considered for both the model based and the within trial analyses. Results will be presented as incremental net benefits (Net benefits = mean WTP - mean cost for each intervention). The intervention with the greatest net benefit would be considered the most efficient. For the model and trial based analyses probabilistic, or stochastic (for the trial based analysis), along with deterministic sensitivity analyses, will be constructed.

8. SAMPLE SIZE AND FEASIBILITY

8.1 Sample size sought

A sample size of n=338 per group is required to provide 90% power to detect a difference in the mean area under the quality of life curve (AUC) of 0.25 standard deviations derived from EQ-5D score measurements, with a significance level of 5% (2-sided alpha). Good data on 24-months AUC for this instrument in this patient group is sparse, but a 0.25 effect size has often been shown to correspond to a worthwhile difference in quality of life measures. This would equate to a difference of 0.1 in the AUC (QALY) assuming a standard deviation of 0.4. Evidence based strategies will be used to enhance questionnaire response rates in this highly motivated group of patients. Conservatively, to allow for 15% non-response in the outcome, it is proposed to randomise 400 subjects in each of the two groups. Such a sample size would provide 90% power to assess differences in the secondary outcome of recurrence between the two surgical techniques from around 10% to around 4%. This magnitude of difference is supported by a recent systematic review which showed a non-statistical trend higher recurrence in the SH group compared to TH group[5].

8.2 Recruitment rates

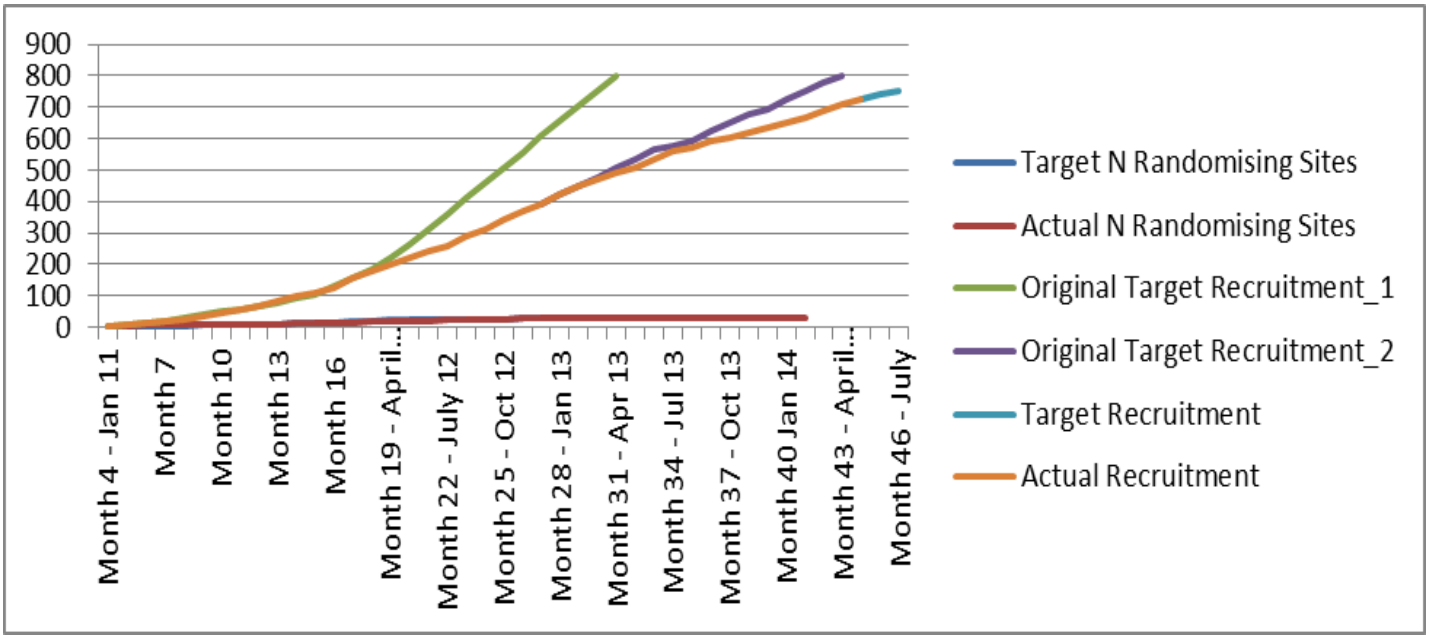
This section pertains to the last time recruitment projections were updated which was on the 2nd of June 2014. Recruitment stopped on the 1st August 2014 with 777 recruited.

Previous experience of recruitment in NIHR/MRC surgery trials co-coordinated from CHaRT, University of Aberdeen suggests that around 50% of those eligible will agree to be randomised. The recruitment period is anticipated to last 43 months (months 4-46 inclusive) and the projection is shown in the figure below. Around 1600 eligible patients are likely to have to be approached to randomise the required 800.

At the outset of the study a staggered recruitment of centres is anticipated, with all centres active by the end of month 20. The first 130 patients will be recruited by month 16, 650 patients by month 28 and the remaining 150 patients by month 31 making a total of 800 patients. The participant recruitment graph in Figure 2 has been modelled to take into account the phased study rollout to the centres from months 1-20.This has been revised to account for recruitment between 4-44 months and completion of 24 month follow-up by end of June 2016.

See Figure 2; projected recruitment chart

Figure 2: Projected recruitment chart



9 ORGANISATION

A detailed plan and timetable of study organisation is given in the Gantt chart (Appendix 2). In summary, 1-3 months - study set up authorisations R&D central staff; months 1-16 – centre recruitment; recruit local staff; months 4-44 - recruit patients staggering centre start up; months 44-70 - all patients recruited (n=800) and complete follow-up (2 months); months 71-72 - close down, analysis, reporting and dissemination.

The Gantt chart (Appendix 2) also shows when we expect the major study events to occur, including meetings. It is anticipated that there will be bi-annual project management meetings, 6 meetings of the TSC and 5 of the DMC. Two meetings are planned for collaborators (including the collaborating colorectal surgeons), the first timed to occur when all the centres have been identified and the second when results are available.

Based on the recruitment projection and the Gantt chart, the specific milestones will be used to allow close monitoring of progress.

9.1 Local organisation in centres

9.1.1 Lead Colorectal Surgeon

Each collaborating centre will identify a lead colorectal surgeon (Principal Investigator (PI)) who will be the point of contact for that centre. The PI will take responsibility for ensuring that the outcome measures are taken consistently and in line with the standardised protocols developed for the study. Specifically this person will:

- Accept overall responsibility for the eTHoS study locally
- Assist the eTHoS Study Office in establishing the study locally (for example agreement from clinical colleagues; helping the main study office to facilitate local Trust approval; identify and appointing a RO and informing all relevant local staff about the study)
- Identify eligible patients
- Explain the eTHoS study and take informed consent
- Take overall lead responsibility for ensuring that the outcome measures are taken consistently and in line with the standardised protocols developed for the study
- Take overall lead responsibility for all clinical aspects of the study locally (for example if any particular concerns occur)
- Notify the eTHoS Study Office of any unexpected clinical events which might be related to study participation
- Provide support and supervision for the local RO
- Represent the centre at the collaborators' meeting
- Place patients who are randomised to SH or TH on the waiting list for surgery
- Complete fully the appropriate eTHoS paperwork for patient participation and
- Facilitate/supervise/participate in the upload of this hardcopy patient data to the web based system.

9.1.2 Recruitment Officer (RO) at each centre

Each collaborating centre will appoint a RO to organise the day to day running of the study in that centre. The responsibilities of this person will be to:

Overall:

- Work with the PI and other local colorectal surgeons in order to organise the day to day recruitment and follow-up of eTHoS participants of the study in that centre
- Keep regular contact with the PI and other colorectal surgeons, notifying them of any problem or unexpected development
- Maintain regular contact with the Study Office (including mailing of relevant material to the Study office)
- Keep local staff informed of progress in the study
- Organise and supervise alternative recruiters in case of holiday or absence and
- Represent the centre at the collaborators' meeting if required.

Specific:

- Assist the PI and other local colorectal surgeons to keep a log of whether eligible participants are recruited or not (with reasons for non-participation)
- Assist the PI and other colorectal surgeons in the distribution of the Patient Information Sheet and the collection and organisation of the patient consent forms
- As appropriate organise follow-up to consultation appointments at 6 weeks after surgery with eTHoS participants
- Ensure timely processing of consent and patient data (complete on-line baseline and follow-up clinical-data collection forms and enter into web application)
- Undertake baseline measurements and follow-up measurements as appropriate and in accordance with eTHoS standard operating procedures
- Support completion (as appropriate) of research questionnaires with the patients both face to face (at baseline) and when required during follow-up, including over the telephone as indicated from the eTHoS Study Office (i.e. in the case of non return or significant missing data)

- Act as a point of contact for the participants at all times and provide information about the trial, as necessary.

9.2 Study co-ordination in Aberdeen

9.2.1 The Study Office Team

The Study Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of study activities. The Data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the study web data entry portal). The Senior IT manager will oversee all IT aspects of the study, while the Senior Trials Manager will provide mentoring and guidance to the trial manager and advice to the team on generic coordination issues. The programmer will create, maintain and update all applications programmes for the trial, including the randomisation application and all administrative and analysis databases. The trial statistician, under the supervision of a Senior Statistician , will be responsible for transacting all statistical elements of the study (including contributing to the pre-specified Statistical Analysis Plan (SAP) and writing the statistical code that will implement this SAP, and producing progress reports for all the study committees (including the TSC and DMC). The economist, under the supervision of a senior economist, will take responsibility for all aspects of the economic evaluations integral to the study. The CHaRT Quality Assurance Manager will ensure that CHaRT's standard operating procedures for trials have been followed and properly documented, including observance of GCP throughout. At the centres, the recruitment coordinators will be responsible for all local processes involved in identifying, consenting and randomising the participants, along with facilitating the delivery of the intervention, under the supervision of the lead colorectal surgeon.

The eTHoS Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting. Finally, we intend to produce a yearly eTHoS Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

9.2.2 The Project Management Group

The study is supervised by its Project Management Group (PMG). This consists of the grant holders and representatives from the Study Office. Observers may be invited to attend at the discretion of the PMG. The PMG will meet/teleconference every six months on average.

The research team has the expertise to cover the clinical and surgical aspects of the research. All the consultant surgeons involved have extensive surgical experience of stapled haemorrhoidopexy. Messrs Loudon (Cochrane review), Jayne (HTA systematic review) and Watson have experience in the design and conduct of RCTs involving SH. Messrs Loudon, Jayne, Maw and Brown have published extensively on SH. Messrs Watson, Loudon, Jayne and Brown are SH trainers.

9.2.3 The Trial Steering Committee

The study is overseen by an independent Trial Steering Committee. The other members are the grant holders. Observers or members of the host university (Aberdeen) and the funders (HTA) may also attend, as may other members of the Project Management Group or members of other professional bodies at the invitation of the Chair. Terms of reference for the TSC can be accessed upon request from the eTHoS study office.

9.3 Research Governance, Data Protection and Sponsorship

9.3.1 Research Governance

The trial will be conducted according to the principles of Good Clinical Practice provided by the MRC guidelines, the detail of which can be viewed at the following link:
http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/
or in line with local implementation of Research Governance to at least the standard of the Aberdeen University policy on Research Governance which can be viewed at the following link:
http://www.abdn.ac.uk/staffnet/governance/research-governance-278.php

9.3.2 Sponsorship
NHS Highland and the University of Aberdeen are the co-sponsors for the trial.

9.3.3 Data Protection
The trial will comply with the Data Protection Act 1998 and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses.

All data collected and stored within the study will comply with the Data Protection Act.

9.4 Data and safety monitoring
9.4.1 Data Monitoring Committee
A separate and independent Data Monitoring Committee (DMC) will be convened. It is anticipated that the members will meet once to agree terms of reference and on at least three further occasions to monitor accumulating data and oversee safety issues. This Committee will be independent of the study organisers and the TSC. During the period of recruitment to the study, interim analyses will be supplied, in strict confidence to the DMC, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials. In the light of these interim analyses, the DMC will advise the Steering Committee if, in its view, there are any ethical or safety issues that may necessitate modification to the protocol or closure of the trial.

The TSC, PMG, clinical collaborators and study office staff (except those who supply the confidential analyses) will remain ignorant of the interim results.

The frequency of interim analyses will depend on the judgement of the Chairman and other independent DMC members. We anticipate that there might be two interim analyses and one final analysis.

9.4.2 Safety concerns
Haemorrhoidal surgical treatment is a very common surgical procedure performed routinely by colorectal surgeons. However, as with all colorectal surgery, there are potential complications (see section 4.4.) and these will be carefully monitored throughout the study.

In terms of general hazards of undertaking a large multi-centre RCT, all of (i) the safety of the participants (ii) the scientific integrity of the study and (iii) value for money for the public funder has been safeguarded by having the following (a) a formal Clinical Trial Risk Assessment carried out by the University of Aberdeen and NHS Highland in their role as sponsors (b) an excellent track record of the applicants in delivering successful multi-centre trials (c) the support of a dedicated UKCRC registered Trials Unit (CHaRT at University of Aberdeen) and (d) excellent governance of the trial conduct by an experienced internationally recognised TSC and DMC.

Collaborators and participants may contact the chairman of the TSC through the Study Office about any concerns they may have about the study. If concerns arise about procedures, participants or clinical or research staff (including risks to staff), then these will be relayed to the Chairman of the DMC.

10. FINANCE

The study is supported by a grant from the National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme - Project Number 08/24/02.

11. ANCILLARY STUDIES

It is recognised, that the value of the study may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advance with the Project Management Group. REC approval will be sought for any new proposals, if appropriate.

12. INDEMNITY

The Patient Information Sheet provides the following statement regarding indemnity for negligent and non-negligent harm:

> 'We do not expect any harm to come to you by taking part in this study. However, if you are harmed by taking part in this research project, there are no special compensation arrangements. 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 normal National Health Service complaints mechanisms (which includes professional indemnity insurance) would be available to you.'

In addition, the universities involved with this study hold and maintain a 'no fault' insurance policy. This policy covers all employees of the universities and those working under their direction.

13. DATA SHARING AND PRESERVATION

The applicants will comply with the data sharing and preservation guidance. The trial statistician (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers in the future to enable meta-analyses.

14. PUBLICATION

The success of the study depends entirely on the wholehearted collaboration of a large number of participants, as well as clinicians including colorectal surgeons and ROs. For this reason, chief credit for the study will be given, not to the committees or central organisers, but to all those who have collaborated in the study. The eTHoS study authorship policy is available Appendix 1. The results of the study will be reported first to study collaborators. The main report will be drafted by the Project Management Group and circulated to all clinical coordinators for comment. The final version will be agreed by the TSC before submission for publication, on behalf of all the eTHoS collaborators.

To safeguard the integrity of the main trial, reports of ancillary or satellite studies will not be submitted for publication without prior agreement from the Project Management Group.

We intend to maintain interest in the study by publication of eTHoS newsletters at intervals for participants, staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final eTHoS Newsletter to all involved in the trial.

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APPENDICES

APPENDIX 1 eTHoS AUTHORSHIP POLICY

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the International Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The eTHoS Study Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the by line 'Jane Doe and the Trial Group'[,2]. Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the by line would read 'Jane Doe *for* the Trial Group')[2].

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. Each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.

ii. Participation must include three steps:

- conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
- drafting the article or revising it for critically important content; AND
- final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself. Those persons who have contributed intellectually to the article but whose contributions do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible.[1] These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

PUBLICATION ARISING FROM eTHoS TRIAL – OPERATIONALISING AUTHORSHIP RULES

We envisage two types of report (including conference presentations) arising from the eTHoS study and its associated projects:

i. *Reports of work arising from the main* eTHoS *study* - If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The eTHoS Study Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the eTHoS Study Group'.
ii. *Reports of satellite studies and subsidiary projects* - Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules, should be recognised in the Acknowledgement section. The role of the eTHoS Study Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the eTHoS Study but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the eTHoS Study Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the eTHoS Study including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from eTHoS is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertakes to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

REFERENCES

1. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*, **104**, 269-274.
2. Glass RM (1992). New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. *Journal of the American Medical Association*, **268**, 99.

APPENDIX 2 Gantt Chart