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HollAND trial: comparison of rubber band ligation and haemorrhoidectomy in patients with symptomatic haemorrhoids grade III: study protocol for a multicentre, randomised controlled trial and cost–utility analysis

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ABSTRACT

Introduction Haemorrhoidal disease is one of the most common anorectal disorders, which affects nearly half of the general population. Treatment of grade III haemorrhoids consists initially of conservative measures, followed by rubber band ligation and haemorrhoidectomy when unsuccessful. Given the current guidelines and numerous modalities the obvious question which needs to be answered is which treatment is the best for grade III haemorrhoids. There is a need for evaluating treatment from the patient's point of view and transparency in surgical and non-surgical treatment outcome.

Methods and analysis This multicentre, randomised controlled, non-inferiority trial with cost–utility analysis compares haemorrhoidectomy with rubber band ligation. Patients aged 18 years and older with symptomatic haemorrhoids grade III are recruited. Primary outcome measure is quality of life at 24 months measured with the EQ-5D-5L and in-hospital (in)direct costs and out-of-hospital postoperative costs. A key secondary outcome is recurrence at 1-year postprocedure. Secondary outcomes are complaint reduction with proctology-specific patient-reported outcome measurements (Haemorrhoid Severity Score, ProctoPROM, PROM-HISS, vaizey score), resumption of work, pain and complication rates. Data are collected at seven different time points. Standard postprocedural care is followed.

A sample size has been calculated using a one sided alpha of 0.025 and a power of 80% with an SD of 0.15 and a non-inferiority limit of 0.05. With stratification by centre and to adjust for 10% lost to follow-up the total sample size will be 360 patients in total (180 per group).

Data will be analysed according to the intention-to-treat and the per-protocol principle.

Ethics and dissemination The protocol has been approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centres, location AMC. Findings will be disseminated in peer-reviewed journals and presented at conferences, whether they are positive, negative or inconclusive.

Trial registration numbers NCT04621695, NTR8020

Strengths and limitations of this study

- ► This study addresses a knowledge gap regarding the optimal treatment of grade III haemorrhoids.
- ► Outcomes are not only based on clinical outcomes but also proctology-specific patient-reported outcome measurements and cost–utility.
- ► As it is an evaluation of existing standard care, both Milligan-Morgan and Ferguson technique as well as rubber band ligation are not further standardised.
- ► It will prove to be challenging counselling patients to participate in a randomised controlled, given the choice between invasive and non-invasive treatment.

INTRODUCTION AND RATIONALE

Haemorrhoidal disease is one of the most common anorectal disorders which affects nearly half of the general population.[1] In the Dutch population, the prevalence is 13 per 1000 patients per year.[2] Symptoms vary from blood loss, itching, soiling and prolapse and can be having a substantial impact on patients activities. Haemorrhoids are described most often by the Goligher classification: a universally used classification focusing on the degree of prolapse.[3] However, in a large colonoscopy-based study, no significant association could be demonstrated between haemorrhoid grade and haemorrhoid symptoms.[1] Treatment consists initially of conservative measures such as lifestyle advice, diet and toilet behaviour.[4] In addition, various surgical procedures are possible, of which haemorrhoidectomy is considered the gold standard, an assumption recently confirmed in a British trial.[5] The most commonly used, low-invasive procedure is the rubber band

ligation (RBL). With better understanding of origin and pathogenesis of haemorrhoids new surgical techniques were developed. In haemorrhoids III the current national guideline advised to treat either by haemorrhoidectomy or by RBL. If symptoms persist after four sessions of RBL than haemorrhoidectomy should be considered. Evidence for this policy is however low grade. The guideline is also not specific on residual complaints and doesn't adequately address the patients related aspects. Given the current numerous modalities the obvious question which needs to be answered is which treatment is the best. A systematic review of three small heterogeneous trials concludes that RBL leads to recurrence more often, but on the other hand is accompanied by less pain and with fewer complications and a lesser burden for the patient.[6] It is also unclear which of the two most common procedures, namely the open haemorrhoidectomy and the RBL, is preferable from a health economic point of view. There are hardly any studies that have looked at the cost-effectiveness of the various treatments. Only study compared stapled haemorrhoidopexy with RBL, favouring RBL.[7] Another recent trial, published in 2016, compares haemorrhoidal artery ligation (HAL) with RBL, with HAL clearly entailing the most costs, even though the analysis includes the chance of repeated RBL treatments.[8] Results from recent trials suggest that haemorrhoidectomy and repeated RBL are effective in treatment of grade II and III haemorrhoids.[5 8] An interesting conclusion from a recent systematic review regarding operative procedures for haemorrhoidal disease is that all procedures have their own advantages and disadvantages.[9] Therefore, items like patient expectations and priorities and costs should be taken into account when deciding which procedure to advice and perform. There is a need for evaluating treatment from the patient's point of view and transparency in surgical and non-surgical treatment outcome. So far there is no sufficiently large trial that meets that demand. A recent national survey among Dutch surgeons with expertise in haemorrhoidal disease demonstrated varying practices in treatment of haemorrhoids.[10] A similar survey was conducted in Italy including more than 32 000 patients.[11] Although (and maybe because of) the most frequently used treatment modalities differed from the ones in the Dutch study the conclusion is the same: necessity of developing practical (Dutch and European) guidelines for treatment of haemorrhoidal disease. Therefore, a well-designed study is essential to compare efficacy and safety of repeated RBL and haemorrhoidectomy for grade III haemorrhoids in a multicentre randomised setting.

Hypothesis

Because RBL is a lesser burden on patients, the hypothesis is that RBL performed in two sessions is not inferior compared with haemorrhoidectomy on quality of life (QOL) in patients with grade III haemorrhoids.

METHODS AND ANALYSIS

Study design

The HollAND trial concerns a randomised, controlled, multicentre non-inferiority trial comparing RBL with haemorrhoidectomy for treatment of grade III haemorrhoids. This trial was registered at the Dutch Trial Registry (NL8020) and at ClinicalTrials.gov (NCT04621695) prior to the start of inclusion. The protocol was drafted in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statements.[12] Patients will be accrued by all ten participating clinics. The design involves allocation of all appropriate consecutive patients with symptomatic grade III haemorrhoids to either RBL or haemorrhoidectomy. After eligibility has been established and patient details noted patients will be randomised to either one of the treatment groups. Assignment to one of the two groups is not blinded. Data will be analysed on 'intention to treat' basis in case patients are not subjected to the randomised treatment modality.

Import changes to methods after trial commencement

Recruitment commenced on 8 October 2019, and, following this, in response to early observations, changes were made to the protocol and trial methods.

In August 2020 (substantial amendment 8, protocol V.8.0), a change was made to the eligibility criteria to not exclude patients using oral anticoagulants. This following a site set up visit where the principal investigator mentioned the amount of excluded patients as a result of this exclusion criterion.

Eligibility criteria

Inclusion criteria

- Haemorrhoids grade III (Goligher classification).
- Age 18 years and older.
- Sufficient understanding of the Dutch written language (reading and writing).

Exclusion criteria

- Previous rectal or anal surgery with the exception of RBL.
- Previous surgery for haemorrhoids (at any time).
- More than one injection treatment for haemorrhoids in the past 3 years.
- More than one RBL procedure in the past 3 years.
- Previous rectal radiation.
- Pre-existing sphincter injury.
- Inflammatory bowel disease.
- Medically unfit for surgery or for completion of the trial (ASA classification >III).
- Pregnancy.
- Hypercoagulability disorders.
- Patients previously randomised to this trial.
- Not able or willing to provide written informed consent.

Sample size calculation

The sample size calculation is based on a non-inferiority design. The primary outcome of the study is

quality-adjusted life-years (QALYs). We have used the result from an earlier study in which RBL was compared with HAL, which is similar to haemorrhoidectomy.[13] For the sample size calculation, we hypothesised an equal QALY between the two groups. Using a one-sided alpha of 0.025 and a power of 80% with an SD of 0.15 and a non-inferiority limit of 0.05, a total amount of 142 patients are needed in each treatment arm. To account for the stratification by centre, by using an intraclass correlation of 0.01 and 15 patients per centre, this number was increased to 162 patients per treatment arm. To adjust for 10% lost to follow-up the total sample size will be 360 patients in total.

Investigational treatment

Rubber band ligation

RBL, first described by Barron, is performed by a suction device that allows a rubber band to be applied at the base of the haemorrhoid via a proctoscope. Maximal suction force used is 40 mm Hg. A maximum of 3–4 bands are used per session. This rubber band constricts the blood supply causing it to become ischaemic before being sloughed approximately 1–2 weeks later. The resultant fibrosis reduces any element of haemorrhoidal prolapse that may have been present. No sedation is required for this day-care procedure. Patients are asked to administer an enema 2 hours prior to the procedure. This is a very commonly performed procedure in all participating clinics.

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. The procedure is performed under either general or spinal anaesthesia in a day-care setting. Patients were asked to administer an enema 2 hours prior to the procedure.

Main study endpoint

Primary outcome measure is QOL at 24 months measured with the 5-level EQ-5D version (EQ-5D-5L) with Dutch rating; in-hospital direct and indirect costs and out-of-hospital postoperative costs (measured with EQ-5D-5L and cost incremental analysis).

Secondary study endpoints

Key secondary outcome

This is recurrence at 1-year postprocedure. Recurrence will be defined the same as in a systematic review and recent clinical trial.[6 13] A patient's self-reported assessment with a dichotomous question will be asked at 6 weeks and at 6, 12 and 24 months: 'At the moment, do you feel your symptoms from your haemorrhoids are[1]: cured or improved compared with before treatment; or[2] unchanged or worse compared with before treatment?'

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

Patient-reported outcomes

To measure QOL (at 12 months) and functional outcomes, several questionnaires will be used (table 1); the EQ-5D-5L and the Vaizey faecal continence score[14] to assess severity of faecal incontinence. Complaint reduction is assessed by the Hemorroid Symptom Score (HSS),[15] the proctology patient-reported outcome measurement (proctoPROM)[16] and Patient-Reported Outcome

Table 1 Trial scheme with planning QOL and PRO questionnaires

	Baseline	Day 1	1 week	6 weeks	6 months	12 months	24 months
EQ-5D-5L	•	•	•	•	•	•	•
ProctoPROM	•		•	•	•	•	•
PROM-HISS	•		•	•	•	•	•
Rome IV criteria	•						
HSS	•			•	•	•	•
Vaizey faecal continence score	•			•	•	•	•
iMCQ				•	•	•	•
iPCQ				•	•	•	•
Analgesia		•	•	•			
Patient-reported recurrence				•	•	•	•
VAS pain		•	•	•			
Return to work			•	•			

EQ-5D-5L, 5-level EQ-5D version; HSS, Hemorroid Symptom Score; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost Questionnaire ; PRO, patient-reported outcome; proctoPROM, proctology patient-reported outcome measurement; PROM-HISS, Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score; QOL, quality of life; VAS, Visual Analogue Scale.

Measurement-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) which are all proctology-specific patient-reported outcome measurements. The procto-PROM is a validated questionnaire consisting of five questions concerning patients well-being. The PROM-HISS is recently developed in Maastricht (the Netherlands) and relates the symptoms.[17] Postprocedural pain was also scored by a Visual Analogue Scale.

Participants are asked to complete the questionnaires at baseline, day 1, 1 and 6 weeks and 6, 12 and 24 months (table 1). These will be sent to them by email and access to a web tool (Castor) will be provided. If the patient does not have an email account, the questionnaires will be send to the patients' home addresses, accompanied by a return envelope provided with postage stamps and the address of the hospital. They are given the opportunity to fill out the forms on a secure participant portal within the trial website. In case of unreturned forms, participants will be contacted by email or telephone to obtain the missing data.

Clinical outcomes

Complications, need for further treatment, absence from work.

Randomisation

After fully signed written informed consent (online supplemental appendix 1), patients will be randomly assigned to be treated by either RBL or haemorrhoidectomy. Following full written consent, baseline data will be collected and patients will be randomly allocated in a 1:1 ratio to either treatment. Neither the recruiters nor the trial project group will be able to access the randomisation sequence. Randomisation will be done web based using Castor. The randomisation sequence will be computer generated. A unique record number will be generated and the allocation will be disclosed. To achieve a balanced distribution of the treatments among participating centres, randomisation will be stratified.

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 in the study database.

Patient and public involvement

The patient organisation Bekken4all was consulted in the initial preparation phase of the study proposal to make sure that this considered relevant in a patients perspective. The patient organisation is actively involved in further preparing the study protocol. Special attention is paid to patient load of the trial and to patient related outcome. Furthermore the patient organisation assisted in preparing patient information. A contact person was installed whom participants can address in case of questions. Several meetings are organised during inclusion to assure progress; another meeting when analysing results and a final meeting when preparing conclusive paragraphs and implementation.

Participant time line

During the preparation phase (3–6 months), the logistic infrastructure of the trial was set up in collaboration with all participating centres and the patient federation. Eligible patients are recruited in 10 hospitals across the Netherlands. Inclusion started in October 2020 in the Proctos Kliniek as first centre after which other participating centres followed. It is expected that around 50% of those eligible will agree to be randomised. From experience, recruitment rate will always be lower than anticipated, therefore, rate of inclusion has been set at the lower rate of inclusion speed. Trained research personnel will take care of and assist with inclusion, randomisation and data synthesis, so that adequate data collection is maximised and warranted. Based on these numbers, the recruitment period is anticipated to last 12–18 months. It is estimated that 360 patients will have been randomised and included by then. The follow-up period will be 24 months. The data analysis phase is expected to be finalised in 6 months.

Recruitment

It is recognised that when given the choice between a non-invasive and an invasive medical procedure, a substantial proportion of patients may choose the non-invasive procedure. Therefore, in order to maximise recruitment patients will be screened before randomisation. During a consecutive telephone recruitment appointment or an email information will be given and patient's treatment preference will be explored. This appointment is regarded as an integral part of the information exchange necessary for informed decision making. Using this approach, rate of recruitment will also be optimised. A log of these screening appointments will be kept.

A research nurse/consultant in every participating centre, responsible for the support and care of patients in the trial, may further improve accrual rate.

Data collection

All medical, QOL and cost data will be collected at the individual hospitals before central collection into the trial database. Data collection will be facilitated by case record forms in Castor. No hospital patient identification numbers will be revealed to the coordinating centre. All patient data are coded and identified by means of a randomisation number. This randomisation number does not include initials or date of birth from the patient. The local investigator will have a decoding list with randomisation numbers and hospital patient identification numbers of his patients in the investigator site file. At each trial operation/procedure, the performing surgeon(s) are noted in the case record form.

In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (WMO), the investigator will inform the subjects and the reviewing

accredited medical ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Statistical analysis

Data will be analysed according to the intention-to-treat and the per-protocol principle. No interim analysis is planned. Analyses will be done using SPSS V.26.0. The primary outcome and key secondary outcome, namely QOL and recurrence, will be analysed using a one-sided alpha with a significance level of 0.025. Descriptive methods will be used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data will be analysed with histograms. The mean difference in the QALYs between the two groups will be assessed through linear regression in which stratification factor (participating centre) will be included, together with the lower bound of the 95% CI. If the lower bound of the 95% CI is higher/less negative than −0.05 QALY difference and the 95% CI does not include this non-inferiority limit in both the intention to treat and per-protocol analysis, non-inferiority is considered proven for this endpoint. The non-inferiority boundary for recurrence at 1-year postprocedure is set on a difference of 10%. RBL performed in two sessions will not be inferior compared with haemorrhoidectomy only when the primary outcome appear to be non-inferior in both the intention-to treat and the per-protocol analysis. Patients excluded from the per-protocol analysis will be those who non-complied with eligibility, missed windows, consent and treatment issues, which included patients who did not receive their allocated treatment. Secondary outcomes will be described by reporting differences with 95% CIs and will be analysed using either a two-sided t-test or Mann-Whitney U test for continuous data and a χ^2 test for categorical data. A $p<0.05$ is considered a threshold for significance. With several questionnaires on different time points, a mixed model will be used to analyse repeated measurements.

Some missing data can be expected, we will use multiple imputations when more than 5% data is missing. If missing data are at random, this will be handled through multiple imputations with predictive mean matching.

Cost-effectiveness analysis

General considerations

We hypothesised that RBLs is non-inferior to a haemorrhoidectomy for the outcome QOL. The economic evaluation of RBLs against haemorrhoidectomy will be performed as a cost–utility analysis (CUA) from a societal perspective with the cost per QALY as the main outcome measurement. The CUA can be used for policy making and composition of a guideline. We will base the CUA on a time horizon of 24 months, because we expect that differences in health outcomes and costs will be presented in the first 24 months. No discounting of effects and costs will be done. Furthermore, a CUA with a lifelong time horizon will be made using extrapolation and model based techniques. To account for uncertainties, a probabilistic sensitivity analysis will be performed.

Incremental cost-effectiveness ratios will be calculated as the difference in costs per QALY sampling variability in the 24 months time horizon. CUA will be accounted for by bias-corrected and accelerated non-parametric bootstrapping. Results will be reported along with their 95% CIs and displayed graphically with cost-effectiveness planes and with cost-effectiveness acceptability curves. One-way and multiway sensitivity analyses will be done for the unit costs of healthcare.

Cost analysis

Medical costs, patient costs and productivity losses will be included in the evaluation. The medical costs cover the costs of surgery, anaesthesia, theatre, perioperative materials, inpatient stay at the ICU and the wards and medications. The patient costs include out-of-the pocket expenses like over-the-counter medication and healthcare related travel costs. Productivity losses are costs resulting from being absent and decreased productivity during work.

Hospital healthcare utilisation will be retrieved from case report forms (CRF) and hospital information systems. Data on out-of-hospital healthcare will be gathered with the iMTA Medical Consumption Questionnaire adjusted to the study setting. The productivity losses will be documented with the iMTA Productivity Cost Questionnaire. Questions on out-of-pocket expenses will be added to these patient questionnaires. Patients will be asked to fill in questionnaires at 1 week, 6 weeks, 6, 12 and 24 months after inclusion in the study.

Costs will be price indexed based on Consumer Price Indices. Costs will be calculated for individual patients as the product sum of the resource use and the respective unit costs.

Patient outcome analysis

Patients will be asked to complete the EQ-5D-5L health status questionnaire at 1 week, 6 weeks, 6, 12 and 24 months after randomisation. These questionnaires will be included in the CRFs. The EQ-5D-5L scoring profiles can be converted into a health utility score based on general population based Dutch tariffs.[18] QALYs will be calculated for each patient after linear interpolation between the successive health utility assessment over time.

Budget impact analysis

General considerations

The budget impact of RBLs compared with haemorrhoidectomy will be assessed from governmental and insurer perspectives in accordance with the ISPOR guidelines.[19 20] The governmental perspective will be from both the broad societal perspective as well as the budgetary healthcare framework (BKZ) and can be used to help setting priorities in healthcare optimisation. The insurers

perspective can be used to examine the net financial consequences of treating third degree haemorrhoids by two sessions of RBL first. The budget impact analyses can be used to guide reimbursement decisions and price and volume negotiations between insurer and healthcare provider.

The budget impact study will reflect the net savings of RBLs compared with haemorrhoidectomy. The time horizon of the budget impact will be 3 years and will be presented per year.

Several scenarios will be examined, full implementation, partial implementation (50%, 75%) and gradual implementation over the years. Sensitivity analyses will be performed for the percentage of patients in which the RBL will be performed as well as sensitivity analysis for differences in number of patients with a relapse.

Cost analysis

For the budget impact analysis from a governmental societal perspective the most recent guidelines for (unit) costing in healthcare research will be applied.[21] In case of impact assessments concerning premium financed healthcare and from the insurer perspective, existing tariffs at the time of analysis will be used (Diagnose Behandel Combinatie costing).

Other study parameters

Baseline characteristics will be collected and described with frequencies (numbers, mean or median with, respectively, percentages, SD or quartiles). Differences between groups will be analysed using independent Student's t-test for normally distributed numerical data, Mann-Whitney U tests for not normally distributed numerical data and χ^2 testing for categorical data.

ETHICS AND DISSEMINATION

Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the WMO and other European guidelines, regulations and acts such as the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG). The protocol has been approved by the Medical Ethics Review Committee (MERC) of the Amsterdam University Medical Centres, location Academic Medical Centre (AMC). Findings will be disseminated in peer-reviewed journals and presented at conferences, whether they are positive, negative or inconclusive.

Recruitment and consent

The informed consent procedure should be performed by the treating physician or a representative that is aware of the details and complications of both treatments included in the trial. Therefore, it is the trial's preference that the consent is taken by the treating physician. The information offered to the patient or representative contains:—a statement that the trial involves research—a full and fair explanation of the procedures to be followed—a full explanation of the nature, expected duration and purpose of the study—a description of any reasonable foreseeable risks or discomfort to the patient—a description of any benefits which may reasonably be expected—a statement that patient data will be handled with care and confidentiality and the period of time the data is saved (15 years)—a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care. Patients are given ample time to decide whether or not to participate in the study. Minors and legally incompetent adults are excluded from the trial.

Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Methods of dissemination of results

Before starting recruitment the trial protocol will be presented at a meeting of the Dutch Society of Surgery. Initiation of the trial is also made knowledgeable at the website of this same society, as to reach the majority of surgeons/proctologists. When the trial has been completed results will be discussed first during a meeting of the Dutch Society Coloproctology/Surgery. In this session experiences from other surgeons treating haemorrhoids will be heard, plans following the trial outcome will be outlined and practical aspects of implementation will be discussed. This will be followed by presentation of results at the annual meeting of the Dutch Society of Surgeons (Nederlandse Vereniging voor Heelkunde). There will then be enough support to adjust the Dutch proctology guideline. We expect several manuscripts prepared from this research to be published in high impact peer-reviewed journals, including publication of this protocol itself. We will publish the results and a lay summary on the study website on study completion.

The techniques under investigation are techniques that are long-existing and wide spread so no extra training is expected to be required.

The actual behavioural change of the healthcare providers may be, however, hindered by lacking to acknowledge the reason of change/adjustment of treatment. It is not unusual to encounter reluctance on changing long standing habits. Education as proposed is one way to tackle this. Recommendations and education will be implemented in the curriculum of general

surgery and proctology trainees. Another way is to use focus groups of patients sharing their experiences. These experiences will be shared with the patient federation.

Monitoring and safety

Monitoring will be performed in compliance with Good Clinical Practice and other rules and regulations in order to achieve high quality research and secure patient safety. Qualified and independent monitors from the Leading the Change trial agency will have access to the data and source documents of the trial. Based on the Site-Specific Monitoring programme of the Leading the Change trial agency, site evaluation visits will be performed to review the quality of the participating sites. All (serious) adverse events, suspected unexpected serious adverse reactions and any other significant problems are reported to the MERC using an online submission system.

A Data Safety Monitoring Board is not necessary for this study as it compares two already well established treatment modalities for haemorrhoidal disease which will not pose additional risk to the subjects in the study.

Annual progress report and amendments

The sponsor/investigator will submit a summary of the progress of the trial to the accredited MERC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems and amendments. All substantial amendments will be notified to the MERC and to the competent authority.

Public disclosure and publication policy

Main presentations and main publications will be in the name of the study group. This will apply when the 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. In such cases, authorship will be presented by the collective title and there will be a footnote of the names of the people and institutions represented. Other manuscripts, such as describing satellite studies, will have individual authorship. Publication or presentation of data can only be possible when the authors state that the corresponding patients were included in the trial. If a centre violates these rules, exclusion from the trial and exclusion from authorship will be the consequence. Decisions on authorship should be justified to, and require agreement from the project management group. The sponsor will have no influence on implementation of the research and content of publications. Publication of data will not take place until accrual of patients has been completed.

Data sharing statement

Data will be available on reasonable request. This will include deidentified participant data and statistical codes. After an embargo period, the data will be accessible for further research and verification. The request should be made to the corresponding author and will be considered by the HollAND trial project group.

Collaborators The HollAND projectgroup consists of the trial governors: dr I.J.M. Han-Geurts, surgeon Proctos Kliniek and prof dr W.A. Bemelman, head of Surgery AMC;The HollAND Trial Steering Committee: prof dr W.A. Bemelman, dr I.J.M. Han-Geurts, surgeon Proctos Kliniek, dr C.I.M. Baeten, surgeon Groene Hart Ziekenhuis, dr E.R. de Graaf, surgeon Ysselland Hospital, dr S.M.M. de Castro, surgeon OLVG, dr A.H.W. Schiphorst, surgeon Diakonessenhuis, dr S. van Dieren, epidemiologist/statistician department of Surgery AMC.

Contributors IJMH-G, WAB and SvD all contributed to conception and design of this trial protocol. IJMH-G and WAB initiated the project and are de chief investigators. The protocol was drafted by IJMH-G and was refined by WAB. Statistical advice was provided by SvD. LD was responsible for drafting the manuscript. All authors read and approved the final manuscript.

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