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Napoleon Trial Study Grp; Kuiper, Sara Z.; Dirksen, Carmen D.; Kimman, Merel L.; Van Kuijk, Sander M. J.; Van Tol, Robin R.; Muris, Jean W. M.; Watson, Angus J. M.; Maessen, Jose M. C.; Melenhorst, Jarno

Published in:
Contemporary Clinical Trials

DOI:
10.1016/j.cct.2020.106177

Publication date:
2020

Contemporary Clinical Trials 99 (2020) 106177

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Effectiveness and cost-effectiveness of rubber band ligation versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent haemorrhoidal disease (Napoleon trial): Study protocol for a multicentre randomized controlled trial

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ARTICLE INFO

Keywords:
Haemorrhoidal disease
Recurrence
Rubber band ligation
Sutured mucopexy
Haemorrhoidectomy
Quality of life

ABSTRACT

Background: Currently, there is no consensus regarding the best treatment option in recurrent haemorrhoidal disease (HD), due to a lack of solid evidence. The Napoleon trial aims to provide high-level evidence on the comparative effectiveness and cost-effectiveness of repeat rubber band ligation (RBL) versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent HD.

Methods: This is a multicentre randomized controlled trial. Patients with recurrent HD grade II and III, ≥18 years of age and who had at least two RBL treatments in the last three years are eligible for inclusion. Exclusion criteria include previous rectal or anal surgery, rectal radiation, pre-existing sphincter injury or otherwise pathologies of the colon and rectum, pregnancy, presence of hypercoagulability disorders, and medically unfit for surgery (ASA > III).

Between June 2020 and May 2022, 558 patients will be randomized to receive either: (1) RBL, (2) sutured mucopexy, or (3) haemorrhoidectomy. The primary outcomes are recurrence after 52 weeks and patient-reported symptoms measured by the PROM-HISS. Secondary outcomes are impact on daily life, treatment satisfaction, early and late complication rates, health-related quality of life, costs and cost-effectiveness, and budget impact. Cost-effectiveness will be expressed in societal costs per Quality Adjusted Life Year (QALY) (based on EQ-5D-5L), and healthcare costs per recurrence avoided.

Discussion: The best treatment option for recurrent HD remains unknown. The comparison of three generally accepted treatment strategies in a randomized controlled trial will provide high-level evidence on the most (cost-) effective treatment.

Trial registration: ClinicalTrials.gov identifier: NCT04101773

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https://doi.org/10.1016/j.cct.2020.106177
Received 17 June 2020; Received in revised form 9 October 2020; Accepted 13 October 2020
Available online 17 October 2020

1. Background

Haemorrhoidal disease (HD) is a very common anorectal disease with an incidence between 4.4 and 36.4% in the general population [1]. Haemorrhoids have troubled humankind since ancient times and might even have influenced world history. There is considerable indication that the emperor of France, Napoléon Bonaparte, suffered from HD. It has been said that on the day of the decisive battle at Waterloo, Napoleon was afflicted with thrombosed haemorrhoids which impaired his battlefield performance [2,3]. Whether or not the anal ailments of Napoléon cost him the victory on Europe's soil, this trial is forever crowned with his name. HD is defined as the symptomatic enlargement and/or distal displacement of the superior haemorrhoidal plexus and the most used classification is according to Goligher [4]; grade I are haemorrhoids that do not prolapse; grade II are haemorrhoids that prolapse but reduce spontaneously; grade III are haemorrhoids that prolapse and have to be reduced manually; grade IV are haemorrhoids that prolapse and cannot be reduced manually. The main symptoms of HD are bleeding, itching, soiling, pain, and prolapse [5]. The first management step of HD is basic treatment that includes the use of laxatives and a high fibre diet [6,7]. If conservative treatment fails and in case of persistent symptoms, the next treatment modality is often rubber band ligation (RBL), which can be repeated multiple times. RBL is an easy, cheap and outpatient-based procedure [8]. However, 30% of the patients develop recurrent symptoms after basic treatment and repeat RBL [9]. Currently, haemorrhoidectomy is the surgical treatment of choice for persistent grade II HD reluctant to RBL and for grade III and IV HD [10]. The major drawback of this technique is that it may be very painful and costly compared to RBL. A relatively novel, but regularly performed surgical alternative is the sutured mucopexy. Although medical costs of sutured mucopexy are comparable to haemorrhoidectomy, the operation is less painful and requires less recuperation time [1,11]. A systematic review of the literature did not identify randomized controlled trials (RCT) comparing treatment modalities for patients with recurrent grade II or III HD (see Appendix A Search Strategy and Outcomes). The choice of the procedure for these patients is now left to the discretion of the healthcare professional, resulting in potentially undesirable practice variation [12]. The Napoleon trial is the first RCT, worldwide, comparing three generally accepted treatment strategies in recurrent grade II or III HD. It aims to provide high-level evidence on the comparative effectiveness and cost-effectiveness of repeat RBL versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent HD after at least two previous RBL sessions.

2. Methods/design

2.1. Objectives

The primary objective is to compare recurrence and patient-reported symptoms over a period of 52 weeks. The secondary objectives are to compare impact on daily life, treatment satisfaction, early and late complication rates, health-related quality of life, costs and cost-effectiveness, and budget impact.

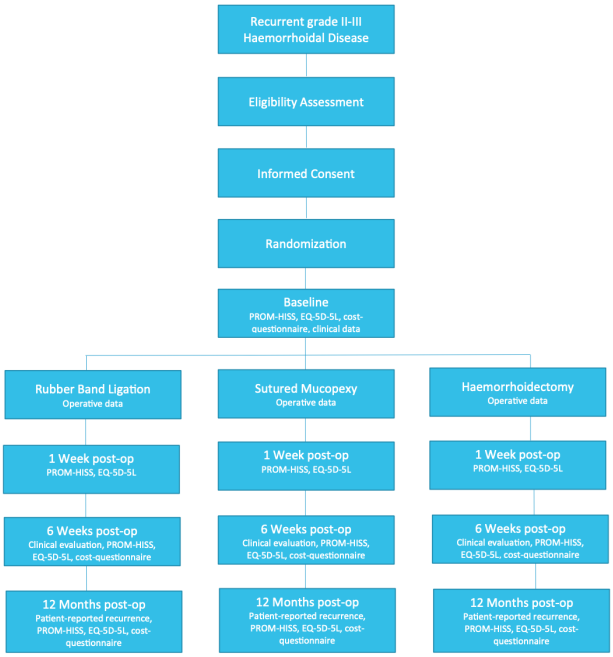

Fig. 1. Flowchart of the Napoleon Trial.

2.2. Study design

The Napoleon trial is a nationwide multicentre, randomized controlled trial (RCT). Patients will be randomly assigned (1:1:1) to receive either RBL, sutured mucopexy, or haemorrhoidectomy (Fig. 1). In total, 16 medical centres in the Netherlands will enrol patients.

2.3. Trial recruitment and allocation

Each medical centre participating in the Napoleon Trial will have a Local Investigator (LI), together forming the Napoleon Collaborative Study Group. All LI's are surgeons and will actively screen patients for eligibility at the outpatient clinic. The Coordinating Investigator (CI) is the central point of contact.

2.4. Study population

Patients can be included if they meet all of the following inclusion criteria:

1. Recurrent haemorrhoidal disease grade II or III according to the Goligher classification
2. At least two rubber band ligation treatments in the last three years
3. Able to complete online questionnaires
4. Sufficient understanding of the Dutch written language (reading and writing)
5. Written informed consent

Patients will be excluded if they meet any of the following exclusion criteria:

1. Previous rectal or anal surgery, with the exception of rubber band ligation
2. Previous surgery for haemorrhoidal disease (at any time)
3. Previous rectal radiation
4. Pre-existing sphincter injury
5. Active diseases of the colon and/or rectum (i.e. active inflammatory bowel disease/diverticulitis/gastro-intestinal malignancy)
6. Medically unfit for surgery or for completion of the trial (American Society of Anaesthesiologists (ASA) classification>III)
7. Pregnancy
8. Hypercoagulability disorders

2.5. Recruitment procedure

Eligible patients will be recruited by the LI at the outpatient department of each participating medical centre. Following normal clinical practice, the LI will inform the patient about the different treatments available for their condition and explains the risks and benefits of all the treatment options. In case a patient is eligible for participation in the study, the LI will discuss the option of participating in the Napoleon Trial and will provide the potential participant with the Patient Information Folder (PIF) and the Informed Consent (IC) form. The patient can take the PIF and IC home to have a chance to read this form extensively. During this time period, the patient has the option to get into contact with the study team to discuss possible participation. According to Good Clinical Practice, a patient is asked for formal consent prior to participation. Patients who decide to participate will send their signed IC form to the participating centre, after which they will be randomly assigned to one of the three treatment arms (Table 1).

2.6. Follow-up procedure

Follow-up will consist of clinical follow-up at six weeks and e-mail questionnaires at baseline, and 1, 6-, and 52-weeks post-procedure. The treating physician will see all patients six weeks post-procedure, as part of standard care. During this clinical evaluation the recovery of the participant will be assessed. The assessment of recurrence will be completed at the end of follow-up, at 52-weeks post-procedure.

2.6.1. Participant withdrawal

The LI or CI can decide to withdraw a participant from the study for urgent medical reasons. Participants can leave the study at any time for any reason if they wish to do so, without any consequences. Withdrawal of participants will be recorded, including the reason.

2.6.2. Randomization and blinding

After written informed consent, participants will be randomized in a 1:1:1 ratio to RBL, sutured mucopexy or haemorrhoidectomy, using randomization stratified by centre, grade of HD (grade II or III HD) and sex, with random permuted block sizes of three and six. A unique record number will be generated and the allocation will be disclosed. Due to the comparison of outpatient-based and surgical treatment strategies in this study, blinding to the treatment allocation for participants and medical staff is not possible. The statistician will analyse the data blinded for treatment allocation.

2.7. Trial interventions

2.7.1. Rubber band ligation

Rubber band ligation (RBL) is a simple, inexpensive procedure. In RBL, a suction device applies a rubber band at the base of each

Table 1
Schedule of enrolment, interventions, and assessments of the Napoleon Trial.

Timepoint (state unit)	t_{-1}	t_0 = baseline	t_1 = intervention	t_2 = 1 week post-procedure	t_3 = 6 weeks' post-procedure	t_4 = 52 weeks' post-procedure
Enrolment:						
Eligibility screening	X					
Informed consent	X					
Allocation		X				
Intervention:						
Rubber band ligation			X			
Sutured mucopexy			X			
Haemorrhoidectomy			X			
Assessments:						
Clinical evaluation		X			X	
Treatment details			X			
Recurrence						X
PROM-HISS		X		X	X	X
EQ-5D-5L		X		X	X	X
Cost-questionnaire		X			X	X
Early complications				X		
Late complications						X

PROM-HISS: Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score, EQ-5D-5L: Euroqol 5D.

haemorrhoidal cushion by using an anoscope [13–15]. The banding process causes necrosis of the banded tissue and as a result the haemorrhoid will shrink. The end result is a return of the haemorrhoidal cushions to a more normal size and configuration, with resolution of haemorrhoidal symptoms [16,17].

2.7.2. Sutured mucopexy

A sutured mucopexy is an operation performed under either general or spinal anaesthesia and was first described by Pakravan and colleagues [18]. The patient is placed in the lithotomy position. A proctoscope is used to give access to the anorectum. Proximal to the dentate line, a *Z*-shaped stitch is placed at the upper level of the haemorrhoidal complex, leaving ample space from the anocutaneous line. Before knotting this Z-shaped suture, a strip of mucosa between both stitches is excised. Then the Z-suture is tightened, pulling up the prolapsing haemorrhoid high into the anal canal. This procedure can be repeated in three to four quadrants of the anus as needed at the point of maximal prolapse [19,20].

2.7.3. Haemorrhoidectomy

Haemorrhoidectomy involves excision of the haemorrhoidal tissue. The procedure is performed under either general or spinal anaesthesia in a day-care setting. A retractor is placed into the anal canal for exposure. An elliptical incision is made in the external haemorrhoidal tissue extending proximally through the dentate line to the upper limit of the haemorrhoids. It removes only the redundant anoderm and haemorrhoidal tissue, leaving the internal and external sphincter muscles intact [21,22]. There are two main excisional procedures currently carried out: open (Milligan and Morgan) and closed (Ferguson). In this trial both techniques are accepted, providing the flexibility for surgeons to undertake whichever procedure is part of their routine practice.

2.8. Harms

In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (WMO), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize a participant's health or safety. The sponsor will notify the accredited Medical Ethical Board without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited board. The CI will take care that all subjects are kept informed.

Adverse Events (AE) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. All AEs reported spontaneously by the subject or observed by the CI, LI, or his/her staff will be recorded.

All Serious Adverse Events (SAE) will be reported in accordance with the guidance from the Central Committee on Research Involving Human Subjects (CCMO). A life-threatening SAE, or SAE with death as a result, will be reported within 7 days after the LI has been informed. Other SAEs will be reported within 15 days.

2.9. Outcomes

2.9.1. Primary outcomes

The primary outcome is recurrence. The definition of recurrent HD is: "reappearance of initial symptoms as reported by the patient", this means "unchanged or worse symptoms of HD compared with before starting treatment". This is in accordance with recently conducted high level RCTs and the European Society of Coloproctology (ESCP) Core Outcome Set (COS) for HD [9,10,23]. Recurrence is assessed using patient's self-report of recurrence at 52 weeks' follow-up, in combination with a patient's report of unchanged or worse symptoms of HD post-procedure derived from the Electronic Patient File (EPF) over the course of 52 weeks.

Our second primary outcome is a patient-reported outcome focusing on symptoms of HD. Symptoms include blood loss, pain, prolapse, soiling and itching, and will be assessed using the Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS). These 5 items are graded using a 5-point Likert scale, ranging from (1) 'none' to (5) 'very much'. The PROM-HISS, together with the other questionnaires, will be completed digitally at four moments during follow-up according to the COS: (1) at baseline; (2) at 1 week; (3) at 6 weeks; and (4) at 52 weeks post-procedure.

2.9.2. Secondary outcomes

Impact of symptoms on daily activities and patient satisfaction with treatment are assessed using the PROM-HISS. Each item is scored on a numeric rating scale from 0 to 10. Regarding impact on daily life, 0 denotes 'no impact at all' and 10 'severe impact on daily life'. For patient satisfaction with treatment this ranges between 0 'not satisfied' and 10 'very satisfied'. Early complications are complications manifested within 7 days post-procedure. Early complications include an 'abscess', assessed by physical examination, and 'urinary retention', assessed by ultrasonography. Complications are considered late complications when recorded at the 52 weeks' post-procedure follow-up. Late complications include 'incontinence', assessed by The Wexner Fecal Incontinence Score, 'anal stenosis', assessed by physical examination, and 'fistula', assessed by MR imaging in case of inconclusive physical examination. Health-related quality of life is assessed using the EQ-5D-5L [24]. It consists of a descriptive system comprising five (health) dimensions and a Visual Analogue Scale (VAS) that records the patient's self-rated overall health. By using an algorithm based on values obtained from the Dutch population index scores (i.e. utilities) for each patient can be calculated. These index scores are combined with length of life to calculate the Quality Adjusted Life Year (QALY). Secondary economic outcomes are costs, cost-effectiveness and budget impact. Total societal costs over the course of 52 weeks will be calculated by multiplying individual-level resource use with the costs per unit. Resource use (e.g. treatment, control visits, visits to the GP, other diagnostic/medical procedures, medication) will be obtained from the Case Report Form (CRF) and from a recall health care resources questionnaire adapted from the Medical Consumption Questionnaire [25] (e.g. over the-counter medication, and lost workdays), filled out at baseline, 6 weeks' and 52 weeks' follow-up.

2.9.3. Data collection and processing

Baseline characteristics will be obtained through the EPF by a member of the local clinical study team and stored in the CRF.

The EPF is screened to assess late complications, re-interventions, re-admissions, duration of medical centre stay and consultations at the medical centre. This will be reported in the CRF.

2.10. Role of the funding source

This project is funded by the Netherlands Organisation for Health Research and Development (*ZonMw*), The Hague [grant number 852002023]. The sponsor does not have any influence on study design, data collection, management, analysis, or interpretation of data. The funding source has no influence on the decision to submit for publication.

2.11. Statistical analysis

Baseline patient characteristics will be presented as means and standard deviations for continuous variables, and as absolute numbers and percentages for categorical variables, stratified by treatment arm. In case of incomplete records, missing data will be imputed using multiple imputation to accommodate intention to treat analysis. The number of imputations will be defined by the percentage of incomplete patients with respect to the variables of interest. Predictive mean matching will be used to draw values to be imputed. An interim analysis will not be

performed for this study, due to the relatively short time span of the study.

2.11.1. Primary study parameters

Differences in the proportion of patients that have experienced a recurrence at 52 weeks after treatment between groups will be tested using Pearson's chi-square test and will be expressed by the percentage of recurrences per treatment arm. Differences between the three groups on the symptom score will be tested using analysis of variance (ANOVA). All analyses will be adjusted for multiple testing using the Bonferroni correction. All three groups will be compared pairwise. To compare PROM-HISS symptom score trajectories after 52 weeks' follow-up between groups, we will use linear mixed-effects regression with random intercept and slope. Covariates will include dummy-variables for the groups, time, and interactions between the groups and time.

2.11.2. Secondary study parameters

Differences between groups on the impact of symptoms on daily activities will be tested with ANOVA corrected for multiple testing using the Bonferroni correction. The occurrence of early and late complications (i.e., complications measured at 1 week or at 52-weeks post-procedure) will be compared between groups using Pearson's chi-squared test. Total costs over the course of 52 weeks will be calculated by multiplying resource use with the costs per unit.

3. Economic evaluation

A trial-based economic evaluation will be performed from a societal and healthcare perspective with a time horizon of 52 weeks, and according to the Dutch guidelines for health economic evaluation [26]. Sources for evaluation of the costs will be cost prices of the Dutch costing manual and cost prices from the Pharmacotherapeutic Compass. Absence of work will be calculated by using the friction cost method, which is recommended by the Dutch manual for costing [27]. Cost-effectiveness will be expressed in societal cost per QALY (based on EQ-5D-5L) and healthcare cost per recurrence avoided. Standard bootstrap and sensitivity analysis will be performed to address uncertainty. Cost-effectiveness acceptability (net benefit) curves will be constructed to visualize the probability of either intervention being cost-effective for a range of threshold values. In addition, a budget-impact analysis (BIA) will be performed in accordance with the Dutch guidelines for economic evaluations and the ISPOR guidelines [28]. The BIA will be performed using a simple decision analytic model. Different scenarios will be compared to investigate various levels of implementation or full substitution of any of the three interventions, as well as the swiftness of implementation (1–5 years). In order to test the robustness of the results, sensitivity analyses will be performed on data input and model assumptions.

3.1. Sample size and feasibility

3.1.1. Sample size

We assume an overall recurrence rate of approximately 30% [10]. We consider a between-group difference of 15% to be of clinical relevance. We need to include 158 patients per group, or 474 in total, to obtain 80% power to detect such a clinically meaningful difference, when using an alpha of 0.05/3, corrected for multiple testing. To accommodate a potential dropout rate of 15%, we will include 186 patients per group or a total of 558 patients. This sample size would provide ample power (>95%) to detect a moderate effect size (defined as Cohen's d = 0.5) on differences in the co-primary outcome, the patient-reported symptom score.

3.1.2. Feasibility

About 50,000 patients are referred to a medical centre for HD in the Netherlands annually, of which roughly half suffer from a recurrence after the first RBL treatment. In most cases, these patients are offered a second RBL, which does not bring relief for one-in-three patients [9]. It is estimated that over 8,000 patients annually are eligible for our study. Bearing these numbers in mind, the aimed sample-size of 558 participants in two years will be feasible.

3.2. Data management

Each participant will receive a unique participant identification code. This code consists of a capital letter (A, B, etc.) indicating centre of inclusion and three numbers (001, 002, etc.) indicating order of inclusion. The study team, the Health Care Inspectorate, the monitors from the external clinical trial organisation and members of the medical ethical committee will have access to the participant data. Data will be stored in a password protected digital database. The CI safeguards the key to the participant identification code and the data. The data will be archived for 15 years after completion of the study. A full Data Management Plan can be obtained through the CI.

3.2.1. Data protection

All data concerning participants or their participation in this trial will be considered confidential and handled in compliance with all applicable regulations. Only members of the study team and LI have access to these data.

3.2.2. Data safety monitoring

Monitoring of the study will be performed by the Clinical Trial Centre Maastricht (CTCM) and is independent from the sponsor and competing interests. It will include checking informed consents, in- and exclusion criteria, reported serious adverse events, and completeness of the CRF. Monitoring includes one site initiation visit, three interim monitoring visits, and one close out visit per centre.

3.2.3. Auditing of the participating medical centres

Auditing will be performed by the CTCM and is independent from investigators and the sponsor.

3.3. Ethical approval

The study is conducted in accordance with the principles of the Declaration of Helsinki, the Medical Research Involving Human Subjects Act (WMO) and the General Data Protection Regulation. The protocol has been approved by the Medical Ethical Committee of the Maastricht University Medical Centre/Maastricht University (METC 19–076). Consent was also obtained from the participating centres.

4. Discussion

To our knowledge, the Napoleon Trial will be the first RCT worldwide comparing RBL, sutured mucopexy, and haemorrhoidectomy in recurrent grade II or III HD aimed at generating high-level evidence of (cost-) effectiveness. Currently, for recurrent grade II or III HD there is no standard treatment. Across the world, HD is a very common disorder, and numerous interventions exist for their management. The most commonly performed therapy is RBL. The literature concerning the efficacy and safety of RBL is substantial [29]. Although it is an easy to perform and relatively cheap option, recurrence rates are high and repetitive banding is often needed [9]. Based on solely the outcome "recurrence rate", the best results are secured with the haemorrhoidectomy. The surgical excision of haemorrhoids has been popular for centuries and has proven to be an effective treatment for merely the more advanced grades of HD [9,30]. The major drawback of this technique is that it is very painful and costlier compared to RBL. A relatively novel surgical alternative is the sutured mucopexy [1,11]. Although medical costs of sutured mucopexy are comparable to haemorrhoidectomy, the operation is less painful and requires less recuperation

time. The recurrence rate of sutured mucopexy is ranked between that of RBL and haemorrhoidectomy. To improve transparency between studies and facilitate the ability to compare and combine (future) studies, an ESCP COS for HD was recently published [23]. In the COS, patient-reported symptoms are selected as the primary outcome to be assessed in all clinical studies on HD. To assess symptoms, our study group recently developed a patient-reported symptom score for HD: The PROM-HISS. The PROM-HISS is based on most reported symptoms in literature and patient interviews [5]. Using this symptom questionnaire as a primary outcome will create awareness among clinicians to take patient's experiences and values into account when making HD treatment decisions. The implementation of the generated data from the Napoleon Trial can facilitate evidence-based treatment in the caretaking of patients with HD in the future and inform guidelines regarding HD.

Availability of the protocol

The full protocol can be obtained from the following link (https://zorgevaluatienederland.nl/evaluations/napoleon-trial). This protocol has been prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), a complete checklist is provided as Appendix B.

Ancillary studies

Not applicable.

Indemnity

The sponsor/investigator has liability insurance, which is in accordance with article 7 of the WMO. This insurance provides cover for damage to research subjects through injury or death caused by the study.

Publication

The results of this study will be disseminated via publications in high-impact scientific journals and presentations on conferences. Both negative and positive results will be published. Results found in this study can inform (inter)national guidelines for the treatment of HD.

Trial status

The start of the Napoleon Trial is currently on hold due to the outbreak of COVID-19.

Contributors

All members of the study group have agreed that all study results will be published. With respects to this, no veto right exists. Before publication, all authors will have the opportunity to give comments on the manuscript. SZK, CDD, MLK and SOB drafted the manuscript. CDD, SMJK MLK, and SOB made substantial contributions to the conception and design of this study and CDD, SMJK, MLK, SOB and AJMW co-authored the writing of the manuscript. All other authors included in the Napoleon Trial Study Group (listed below) participated in the design of the study and are local investigators at the participating centres. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank dr. Alessandro Sturiale (Surgical Centre of Florence, Italy) for providing access to his instruction videos on the sutured mucopexy and the haemorrhoidectomy

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2020.106177.

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