Loose seton prior to surgery for single-tract cryptoglandular fistula vs no seton:

SETON trial

Version 4.0

Januari 14th 2026

PROTOCOL TITLE 'loose seton prior to surgery for single-tract cryptoglandular fistula vs no seton, an RCT'

Protocol ID	NL-010338 • PI-01.01
Short title	SETON-trial
Version	4.0
Date	Januari 14th 2026
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
IMDD	Investigational Medical Device Dossier
METC	Medical research ethics committee Amsterdam UMC (MREC); in Dutch: medisch-ethische toetsingscommissie Amsterdam UMC (METC)
Review committee	Medical research ethics committee (MREC) or CCMO
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Loose seton placement prior to single-tract cryptoglandular fistula surgery is custom practice but evidence of effect on outcome is scarce. If this does not add to better outcome an operative procedure may be avoided which would benefit patients. It would also impact costs of treatment.

Objective: To determine if a loose seton prior to sphincter preserving surgery in patients with single-tract cryptoglandular anal fistula is really necessary.

Study design: The study concerns a randomized multicenter trial with cost-utility analysis comparing loose seton placement followed by sphincter preserving surgery of single-tract non-purulent mid high and high perianal fistula versus surgery without prior seton placement. Patients will be accrued by all participating clinics. The design involves allocation of all appropriate consecutive patients with single-tract midhigh or high cryptoglandular anal fistula to either loose seton placement or direct sphincter preserving surgery. Patients will be randomized to either one of the treatment arms. Assignment to one of the two groups is not blinded. Randomization is performed by computer and will be done through internet. Data will be analyzed on 'intention to treat' basis in case patients are not subjected to the randomized treatment modality.

Study population: Adults 18 years and older with a single tract mid-high or high cryptoglandular anal fistula.

Intervention: Group A: Patients receive a loose seton prior to definitive fistula surgery (two-stage procedure), which is currently considered standard care in the Netherlands.
Group B: Patients proceed directly to definitive surgery without prior seton placement (one-stage procedure).

Main study parameters/endpoints: The main outcome of the study is fistula closure at 26 weeks following the final surgical intervention. Determined through the absence of fistula related symptoms (pain and/or leakage of fluids or pus) and if necessary confirmed with ultrasound or MRI.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The expected burden for participants is minimal and in line with routine clinical practice.

Patients in both groups will receive standard surgical care for perianal fistulas, with the only difference being the presence or absence of a loose seton prior to surgery.
Participants will be asked to complete questionnaires at several time points: at baseline, after surgery, and during follow-up visits (up to 12 months). Any risks are those typically associated with anal fistula surgery (e.g., pain, infection, recurrence), and these are not increased by participation in the study.
The findings will contribute directly to improving evidence-based care and potentially reducing unnecessary interventions.

1. INTRODUCTION AND RATIONALE

Perianal fistulas are a burdensome, often recurrent condition that affects quality of life and can lead to long treatment trajectories. In the Netherlands alone, approximately 5,000 surgical interventions are performed annually for this condition, with over 50% of patients requiring two or more procedures [1]. Mid-high and high fistulas are often treated using a staged approach that begins with the placement of a loose seton before definitive repair.

While the loose seton is commonly used and considered standard care in many centers, there is no high-quality evidence proving its superiority. The European Society of Coloproctology (ESCP) guidelines acknowledge the practice but rate the supporting evidence as weak [2]. Notably, the Dutch national guideline on proctology also lacks a clear recommendation on this topic [1].

Several retrospective studies and systematic reviews suggest that while setons may aid in fistula management, their role in improving surgical outcomes remains uncertain. Mitalas et al. [3] examined seton drainage prior to advancement flap repair and concluded that there was no added benefit with preoperative seton drainage compared to without.

The core issue is that while the loose seton may provide theoretical advantages (e.g., tract maturation, infection control), there is no definitive proof that it leads to improved fistula closure rates or functional outcomes. Moreover, the use of a seton introduces an additional procedure, prolongs the treatment course, and may lead to discomfort and inconvenience for the patient. From both a clinical and economic perspective, it is essential to determine whether this commonly used step is actually necessary.

This research is timely and socially relevant, as it has the potential to refine standard care, reduce unnecessary interventions, and improve patient experience and cost-effectiveness.

2. OBJECTIVES

Primary Objective:

The main outcome of the study is fistula closure at 26 weeks following the final surgical intervention. Determined through the absence of fistula related symptoms (pain and/or leakage of fluids or pus) and if necessary confirmed with ultrasound or MRI.

Secondary Objective(s):

- Patient-reported outcome measures (PROMs): Vaizey incontinence score and FIQL (Fecal Incontinence Quality of Life scale)
- Clinical outcomes: fistula recurrence, postoperative complications, need for re-interventions, pain intensity (VAS score), return to work
- Quality of life: Measured at 12 months using the EQ-5D-5L
- Both in-hospital direct and indirect costs will be analyzed using EQ-5D and incremental cost analysis
- Out-of-hospital postoperative costs will also be included
- Anal Fistula Core Outcome Set (AFCOS)

3. STUDY DESIGN

The study concerns a randomized multicenter trial with cost-utility analysis comparing loose seton placement followed by sphincter preserving surgery of single-tract non-purulent mid high and high perianal fistula versus surgery without prior seton placement. Patients will be accrued by all participating clinics. The design involves allocation of all appropriate consecutive patients with single-tract mid-high or high cryptoglandular anal fistula to either loose seton placement or direct sphincter preserving surgery. After eligibility has been established and patient details noted patients will be randomized to either one of the treatment arms. Assignment to one of the two groups is not blinded. Randomization is performed by computer and will be done through internet.

For the primary non-inferiority analysis, outcomes will be analyzed both on a per-protocol basis and an intention-to-treat basis, with the per-protocol analysis being leading for the non-inferiority assessment.
For the assessment of superiority, both intention-to-treat and per-protocol analyses will be performed.

A non-inferiority design is chosen to test whether skipping the seton step is just as effective, while potentially reducing the treatment burden. The study will run for 36 months, including preparation, recruitment, follow-up, and analysis.

4. STUDY POPULATION

4.1 Population

The study population consists of adults with a single-tract mid-high or high cryptoglandular perianal fistula, eligible for sphincter-preserving surgery.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- Men and women aged 18 years or older
- Single tract mid-high or high cryptoglandular anal fistula (determined based on medical history, physical examination. In case of doubt and endoanal ultrasound or MRI will be performed.
- Eligible for e-mail questionnaires
- Sufficient understanding of the Dutch written language (reading and writing)
- Obtained written informed consent

4.3 Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- Presence of an anorectal abscess
- Multiple or complex anorectal fistulas
- Diagnosis or history of inflammatory bowel disease (in case of clinical suspicion further investigation will be performed)
- History of anorectal malignancy
- Use of immunosuppressive medication at the time of surgery
- History of pelvic radiation
- Pregnancy or lactation

4.4 Sample size calculation

The sample size calculation is based on a non-inferiority design. As the aim of the study was to assess whether not placing a seton (new treatment) is at least as good as the placing of a seton in the treatment of perianal fistulas, the hypothesis, H0, was 'the new treatment is worse than the old method', whereas the alternative hypothesis, HA, was 'the new treatment is as good as or better than the old treatment'. For power calculations, the margin of difference for the two treatment methods was set at 15 percent. For a power of 80 per cent and level of significance of 5 per cent, 126 patients were needed per group, with a success rate for standard treatment of 60 per cent. Taking a 10% lost to follow up percentage into account, a total of 277 patients is necessary to be included.

5. TREATMENT OF RESEARCH PARTICIPANTS

5.1 Investigational product/treatment

The intervention in this study is the placement of a loose seton for 8 weeks in patients with a single-tract mid-high or high cryptoglandular perianal fistula, prior to definitive sphincter-preserving surgery. A loose seton is a soft surgical thread placed through the fistula tract to promote drainage, reduce inflammation, and prevent premature closure of the external opening before surgery. The comparator is no seton placement, meaning patients undergo direct sphincter-preserving surgery without prior seton use. This represents a one-stage surgical approach.

Both interventions are surgical in nature and reflect current clinical practices. There is no use of a placebo in this study, as the comparison involves two active treatment strategies already used in daily practice.

Seton: Material: silicone vessel loop (diameter approx. 2–3 mm), applied separately (non-cutting), extracutaneous knot. Procedure performed by (or under supervision of) a colorectal surgeon, on an outpatient basis under local anesthesia.

5.2 Use of co-intervention

Not applicable

5.3 Escape medication

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable. This study does not involve any investigational product, medical device, drug, or food supplement. The procedures under investigation (seton placement and surgery) are both considered standard clinical practice

7. NON-INVESTIGATIONAL PRODUCT

Not applicable. This study does not involve any investigational product, medical device, drug, or food supplement. The procedures under investigation (seton placement and surgery) are both considered standard clinical practice.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary outcome is successful fistula closure at 26 weeks after surgery, defined as the absence of external openings or discharge on physical examination. In cases of uncertainty, MRI or endoanal ultrasound will be used to confirm healing.

8.1.2 Secondary study parameters/endpoints

Secondary endpoints include:

- Recurrence rate
- Postoperative complications
- Fecal incontinence (Vaizey score)
- Fistula-related quality of life (FIQL)
- Generic health-related quality of life (EQ-5D-5L)
- Pain score (VAS)
- Time to return to work
- Need for re-intervention
- In-hospital and post-discharge costs (cost-utility analysis)

All outcomes will be reported in line with the Anal Fistula Core Outcome Set (AFCOS).

- Quality of life at 12 months measured with the EQ-5D-5L with Dutch rating. The EQ-5D-5L is a generic Health Related Quality of Life (HRQoL) measure, which is broadly used in economic evaluation. The instrument examines a patient's HRQoL on the day of the interview. It consists of the EQ-5D-5L descriptive system and the EQ-Visual Analogue Scale. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses to the 5 items result in a patient's health state that can be transformed into an index score representing health-related quality of life, ranging between 0 (death) and 1 (full health). These index scores are combined with length of life to calculate the QALY. The EQ-VAS records the patient's self-rated health with endpoints labelled 'the best health you can imagine' at the top and 'the worst health you can imagine' at the bottom.

- In-hospital direct and indirect costs (measured with iPCQ and iMCQ) and out-of hospital postoperative costs.
- Pain will be measured using a Visual Analogue Scale (VAS), where patients rate their pain on a simple line from 0 (no pain) to 10 (worst imaginable pain). This helps us understand how uncomfortable the recovery period is for each approach.
- Recurrence of fistula.
- Fecal incontinence will be assessed using two tools that together give us a fuller picture of how patients are doing. The first is the Vaizey score, which looks at the physical side of things—like how often someone experiences leakage of gas, liquid, or stool, whether they need to rush to the toilet, use pads, or take medication. It also asks how much these symptoms affect daily life. The score ranges from 0 (no problems) to 24 (severe symptoms). Alongside that, we'll use the Fecal Incontinence Quality of Life (FIQL) scale, which focuses more on how living with incontinence affects someone emotionally and socially. It asks about things like lifestyle limitations, feelings of embarrassment, and how people cope. The FIQL scores range from 1 to 4, with higher scores meaning a better quality of life. By using both tools, we can understand not just the medical symptoms, but also how people feel and function in their daily lives.
- Patient-reported symptoms will be evaluated using the proctoPROM(5), a questionnaire developed specifically for people with anorectal conditions. It captures how bothersome symptoms like pain, discharge, or urgency are, and how much these affect daily life. Patients will complete this before treatment and again at 1 and 6 weeks, and 6 and 12 months.
- Clinical outcome measures;
    - Data collected during operation include are code(s) of surgeon(s); date of surgery; type of surgery; blood loss in milliliters; 'skin to skin' operation time; intraoperative complications.

- The following postoperative parameters are collected:
    - Day of discharge from hospital;
    - Complications including death and cause of death within 30 days will be reported using the Clavien-Dindo classification of surgical complications(6).
    - Recurrence within one year.

- Reason and duration of possible readmission in hospital within 90 days postoperatively.
- Duration of absence from work.

	Baseline	Procedure	1 week	6 weeks	6 months	12 months
EQ-5D-5L	x		x	x	x	x
proctoPROM	x		x	x	x	x
Vaizey/FIQL	x			x	x	x
iPCQ				x	x	x
iMCQ				x	x	x

Table 1 Trial scheme with planning questionnaires.

8.1.3 Other study parameters

Baseline values eg: age, gender, body weight, length, smoking, medication

8.2 Randomisation, blinding and treatment allocation

Patients will be seen by the surgeon/consultant and screened for eligibility. This will be noted in a trial log book. If the patient fits the criteria for the study, they'll be given both a verbal explanation and a written Patient Information Sheet that clearly outlines what the study is about, why it's being done, and what participation would involve. They'll have time to think it over, ask questions, and talk it through with others if they wish. If they choose to participate, they'll be asked to sign a consent form confirming they understand the study and agree to take part.

After that, patients will be randomly assigned to one of two treatment groups. One group will first have a loose seton placed before their final surgery (the two-stage approach), while the other group will go straight to surgery without a seton (the one-stage approach). This assignment will be done using a secure online system (Castor EDC).

Because the treatments are visibly different, the study is not blinded — both patients and surgeons will know which approach was chosen.

8.3 Study procedures

All participants in this study will undergo surgery for a single mid-high or high perianal fistula, which is standard care. Depending on their randomization, some patients will have a loose seton placed first, followed by definitive fistula surgery at a later stage (two-stage approach), while others will proceed directly to surgery without a seton (one-stage approach). Both treatments are already commonly used in clinical practice.

To track recovery and outcomes, patients will complete questionnaires at baseline, 6 weeks, 3 months, 6 months, and 12 months. These cover general health, continence, fistula-related quality of life, pain, and patient-reported outcomes.

The primary endpoint — fistula closure — will be assessed at 26 weeks. This will be evaluated during a clinical follow-up visit. If there is any uncertainty, further assessment using MRI or ultrasound will be performed.

8.4 Withdrawal of individual research participants

Participants can leave the study at any time for any reason without any consequences if they wish to do so. The investigator can decide to withdraw a participant from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal

Not applicable.

8.5 Replacement of individual research participants after withdrawal

Patients who withdrew their informed consent will not be replaced.

8.6 Follow-up of research participants withdrawn from treatment

The statistical analysis is planned according to intention to treat principle. So patients that choose to withdraw from the treatment will be analysed in the group they were allocated to.

8.7 Premature termination of the study

An interim analysis is not planned.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of research participant safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize participant health or safety. The sponsor will notify the review committee 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 review committee. The investigator will take care that all participants are kept informed.

9.2 AEs, SAEs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to surgical treatment of single-tract cryptoglandular anal fistula. All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

Clinical Investigators and ultimately the Principal Investigator (PI) have the primary responsibility for SAE identification, documentation, grading, and assignment of attribution to the investigational device/intervention. All observed or volunteered SAEs, regardless of treatment area or suspected causal relationship to the investigational drug or study treatment(s) will be recorded in the patient file and subsequently in the (e)CRF.

The sponsor will report the SAEs through the web portal *Research Portal* to the review committee that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.4 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable. A DSMB is not necessary for this study as it compares two well-established treatment modalities for cryptoglandular simple fistula in the participating clinics, which will not pose additional risk to the subjects in the study

10. STATISTICAL ANALYSIS

Data will be analyzed according to both the intention-to-treat and per-protocol principles, as required for non-inferiority trials. The primary analysis will focus on the difference in healing rates between groups, using a 95% confidence interval to assess non-inferiority.
Some missing data is expected, we will use multiple imputations when more than 10%, and less than 50% of the data is missing. If missing data are at random, this will be handled through multiple imputations with predictive mean matching.
Analyses will be conducted using SPSS.

10.1 Primary study parameter(s)

The primary outcome of the study, the difference in fistula closure rates between the two groups, will be analyzed according to both the intention-to-treat and per-protocol principles. The difference between groups will be calculated along with the corresponding 95% confidence interval. Non-inferiority will be demonstrated if the lower bound of the confidence interval lies above the 15 percent non-inferiority margin. Differences in QALYs and other patient-reported outcomes (PROMs) will be calculated using linear interpolation between successive time points and presented with 95% confidence intervals.

10.2 Secondary study parameter(s)

Secondary outcomes will be analyzed using either a t-test or Mann-Whitney U test for continuous data and a Chi-Square test or Fisher exact test for categorical data. If missing data exceeds 10% of the data and is missing at random data will be multiple imputed using predictive mean matching. The questionnaires, administered at fixed intervals, will be analyzed using a linear mixed model to prevent multiple testing. The remaining variables (recurrence rate, postoperative complications, need for re-intervention) will be compared at the final follow-up.

Cost effectiveness analyses (CEA)

General considerations:

This study also includes a full economic evaluation comparing the two treatment strategies. We hypothesize that omitting the seton may reduce overall healthcare costs without compromising outcomes. The economic evaluation will be conducted both as a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). In the CEA, the primary outcome will be cost per successfully healed fistula. In the CUA, the outcome will be cost per quality-adjusted life year (QALY). These analyses help determine whether avoiding the seton step is not only clinically safe but also a smarter use of healthcare resources.
Both evaluations will adopt a societal perspective over a 12-month time horizon. A lifelong simulation will also be conducted using Monte Carlo methods to explore long-term cost differences. To address uncertainty, a probabilistic sensitivity analysis will be performed. Incremental cost-effectiveness ratios (ICERs) will be calculated for both healed fistulas and QALYs. Non-parametric bootstrapping will be used to assess variability and 95% confidence intervals will be reported. The results will be visualized using cost-effectiveness planes and acceptability curves. Sensitivity analyses will explore the influence of key cost assumptions.

Cost analysis:
Medical costs, patient costs and productivity losses will be included in the evaluation, the most recent guidelines for costing in healthcare research will be used(7).The cost analysis will include direct medical costs (e.g., surgery, hospital stay, follow-up visits, complications), non-medical costs (e.g., patient travel, over-the-counter medications), and productivity losses (e.g., time away from work). In-hospital data will be gathered from patient records and CRFs, while post-discharge healthcare use and productivity costs will be collected using the iMTA Medical Consumption Questionnaire (iMCQ) and the iMTA Productivity Cost Questionnaire (iPCQ). Questions on out-of-pocket expenses will be added to these patient questionnaires. Patients will complete these at baseline, 3, 6, and 12 months. Costs will be price indexed based on consumer price indices(CPI). Costs will be calculated for individual patients as the product sum of the resource use and the respective unit costs. In the lifelong evaluation a discounting of costs and effects will be done to account for time preferences.

Patient outcomes:
To measure the effect on quality of life, all patients will complete the EQ-5D-5L questionnaire. These scores will be converted into utility values using the Dutch tariff(8), and used to calculate QALYs through linear interpolation over time. The primary clinical outcome — fistula closure — will be recorded from the hospital data.

Budget impact analysis (BIA)

General considerations:

The affordability of omitting routine seton placement in the treatment of high cryptoglandular perianal fistulas will be assessed from both a societal and hospital perspective, following the ISPOR guidelines for budget impact analysis [9,10]. From a societal standpoint, this evaluation explores whether skipping the seton—if shown to be non-inferior—could lead to better resource allocation in the Dutch healthcare system. From the hospital perspective, the focus is on how this shift might affect actual operating budgets.

The analysis will use a 5-year time horizon and will be both incidence- and prevalence-based, reflecting the impact of this change over time. Different implementation scenarios will be modeled: full immediate adoption, phased adoption (e.g., a 25% increase in uptake each year), or partial uptake (e.g., 70%, 80%, or 90% coverage). Sensitivity analyses will explore the influence of variation in patient numbers, cost estimates, and seton usage rates.

Cost analysis:

In the Netherlands, about 5,000 anal fistula surgeries are performed annually [11]. As precise usage rates of seton placement vary and aren't consistently documented in national data, we're conservatively assuming that every one of these patients currently receives a seton. That means approximately 5,000 patients per year would be impacted by this change in practice.

Dutch hospital tariffs and Diagnosis Treatment Combination (DBC) codes estimate the total cost of placing and managing a seton at around €1,000 per patient. This total incorporates the minor procedure (typically €450–€550), materials (€50–€100), one or more follow-up visits (€150–€200), and seton replacements or adjustments in about a quarter of cases (€100–€200) [12].

This translates to around €5 million in annual healthcare costs related to seton use. Beyond this, indirect societal costs also need to be considered. Waiting for definitive surgery due to the seton step may delay recovery and return to work. Assuming that patients in a one-stage strategy return to work just five days earlier on average—and applying a Dutch daily productivity loss of €278 [13]—this could save €1,390 per patient in lost productivity. Across the 5,000 patients, that's an additional €7 million in potential societal savings per year. We expect to avoid a routine seton placement in 500 patients. That would mean a saving of €1620000 annually.

Diversity

No patient will be excluded based on gender or cultural background. We will, posthoc, create subgroups based on gender and age in order to investigate if conclusions from the study apply to all groups. Differences between groups on primary outcome is not expected.

10.3 Other study parameters

Baseline characteristics will be collected and described with frequencies (numbers, mean or median with respectively percentages, standard deviation or quartiles). Differences between groups will be analyzed using Independent Students T-test for normally distributed numerical data, Mann-Whitney U tests for not normally distributed numerical data and chi-square testing for categorical data.

10.4 Interim analysis

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version October 2024), in accordance with the Medical Research Involving Human Subjects Act (WMO) and other European guidelines, regulations and acts such as the GDPR (General Data Protection Regulation, in Dutch: Uitvoeringswet AVG).

This study has been reviewed and approved by the Central Committee on Research Involving Human Subjects (CCMO)

In accordance to section 10, subsection 1, of the WMO, the Investigator will inform the subjects and the reviewing the Central Committee on Research Involving Human Subjects (CCMO) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the clinical trial proposal. The study will be suspended pending further review by the Central Committee on Research Involving Human Subjects (CCMO), except insofar as suspension would jeopardize the subjects health. The study will be conducted according to national and European regulations.

11.2 Recruitment and consent

Participants who meet the in- and exclusion criteria for this study, and present themselves with complaints at the outpatient clinic of the participating centers will be asked to participate. The eligible patients will receive oral and written information about the content of the study from the treating physician. The informed consent procedure will be performed by the researcher or a representative who is trained and aware of the details of the trial. The informer will give the patient the patient information sheet (in Dutch: patiënten informatie folder, PIF). The patient will be given a minimum of 48 hours to read the provided information and informed consent form and ask questions about it. In case of willingness to participate, written informed consent will be obtained. The treating physician or someone from the research team, as well as the patient both have to sign the informed consent form according to the protocol, prior to randomization into the study. Participation in this study is on a voluntary basis. If persons do not wish to participate, they can do so without specifying why. Deciding not to participate in the study will not affect regular treatment and follow-up care. Participants are allowed to withdraw from the study at any time after they have given their written consent, without giving reason. The general practitioner of the patient is informed about the participation in this study.

In the informed consent form, the patient has given their consent to inform their general practitioner if necessary.

Informed consent is obligatory to participate in the study. In the informed consent form a passage requesting consent for the storage of data for use in future research on pilonidal sinus disease is included. In case the storage of data for use in future research is refused, a patient can still participate in the study. Separate informed consent is asked for permission to approach participants for future research.

11.3 Objection by minors or incapacitated research participants

Not applicable

11.4 Benefits and risks assessment, group relatedness

Participants in both groups will be closely monitored. The risk for study-related complications will be relatively low. There is sufficient knowledge on safety and complications because it concerns a standard treatment procedure. Further, patients are asked to fill in questionnaires at 5 different time points (5 x 10 minutes). The potential benefit of receiving no seton would be receiving one less surgical procedure.

11.5 Compensation for injury

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

The sponsor (also) 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 participants 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.

11.6 Incentives

None.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be collected in a web based registry (Castor EDC, www.castoredc.com). The computer will randomly assign an unique numeric code for every subject that bears no relation to initials or date of birth. Data handling will be performed with coded data, with the key (code to personal information linkage) only available to the local investigator and the research nurse working in the local center. Persons who have access to the data include: investigators, research staff, monitoring and quality assurance personal. Data will be preserved for the duration of 15 years. The handling of personal data complies with the EU General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG, UAVG).

12.2 Monitoring and Quality Assurance

An independent monitor from the Amsterdam UMC will monitor study data of the participating centers according to Good Clinical Practice. The detailed description of the onsite monitoring tasks at each participating center will be provided in the study monitoring plan. Due to the negligible risk associated with the study, onsite monitoring will be conducted in select participating centers, rather than all of them. During the onsite monitoring, the informed consent of all participating subjects will be thoroughly reviewed. Additionally, Source Data Verification, which involves comparing data in the Case Report Forms (research forms/questionnaires) to the source data (patient records), will be performed as part of the onsite monitoring process. Data that will be checked are the inclusion and exclusion criteria and the primary outcomes of the study. The monitor will also look at whether all (S)AEs are appropriately reported within the timelines as required by laws and regulations.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the review committee has been given. All amendments will be notified to the review committee that gave a favourable opinion.

Non-substantial amendments will not be notified to the review committee, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the review committee once a year. Information will be provided on the date of inclusion of the first participant, numbers of participants included and numbers of participants that have completed the trial, serious adverse events, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the review committee of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the review committee immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the review committee within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the review committee.

12.6 Public disclosure and publication policy

With respect to publication policy, the CCMO statement will be used. All study results will be published without restrictions. All members of the study group agree that all study results will be published. With respects to this, no veto right exists. Both negative and positive results will be published. Before publication, all authors will have the opportunity to give comments on the manuscript. Data will be published as soon as possible after finishing data analysis. 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 and after finishing data analysis.

The proposed study contributes to evidence-based medicine and the results should become available for routine daily practice. The implementation activities comprise general activities including dissemination activities and adoption of professional guidelines. The existing clinical guideline proctology will be adjusted: recommendations following from this study will be summarized in this guideline. The guideline is available to clinicians, patients, insurance companies and other health care providers. The result of implementation of the proposed study can be measured using the existing registration system. The DBC Information System (DIS) receives and manages information about all treatment processes in hospitals, mental healthcare and rehabilitation care. DIS is administratively and facility accommodated with the Dutch Healthcare Authority (DHA). Healthcare institutions have the legal obligation to provide the DHA with data on treatment. Implementation will further be propagated during annual society meetings of the NVVH (Dutch society of Surgery). The NVMM (Dutch society of Medical Microbiology) will also be contacted and members informed about our results. Resistance against results will be low due to high external validity (academic, top-clinic and general hospitals) which also facilitates implementation nationwide. To ease dissemination education and implementation named investigators and an implementation expert are part of the research group.

A data management plan (DMP) will be composed containing the FAIR principles that makes data: Findable, Accessible, Interoperable and Reusable (FAIR). Existing data will be used and new data will be generated. Data are registered in an archive or repository and open access will be enabled. Results will be disclosed in a peer review medical journal to guarantee transparency. The study protocol will be registered in an open access public trial registry before recruitment.

13. STRUCTURED RISK ANALYSIS

Not applicable

14. REFERENCES

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