BMJ Open

Antibiotic Treatment foLlowing surgical drAinage of perianal abScess (ATLAS): protocol for a multicentre, double-blind, placebo-controlled, randomised trial

Justin Y van Oostendorp ,[1,2] Lisette Dekker ,[1,2] Susan van Dieren,[1] Willem A Bemelman,[1] Ingrid J M Han-Geurts[2]

To cite: van Oostendorp JY, Dekker L, van Dieren S, *et al*. Antibiotic Treatment foLlowing surgical drAinage of perianal abScess (ATLAS): protocol for a multicentre, double-blind, placebo-controlled, randomised trial. *BMJ Open* 2022;**12**:e067970. doi:10.1136/bmjopen-2022-067970

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-067970).

Received 01 September 2022
Accepted 17 October 2022

[1]Department of Surgery, Amsterdam UMC Location AMC, Amsterdam, The Netherlands
[2]Department of Surgery, Proctos Kliniek, Bilthoven, The Netherlands

Correspondence to
Justin Y van Oostendorp;
j.oostendorp@amsterdamumc.nl

ABSTRACT

Introduction Perianal fistula is a burdening disease with an annual incidence of 6–12/100 000 in Western countries. More than 90% of crypto-glandular fistulas originate from perianal abscess. Despite adequate drainage, up to 83% recur or result in an anal fistula, the majority developing within 12 months. There is some evidence that gut-derived bacteria play a role in the development of perianal fistula. Up till now, it is not common practice to routinely administer prophylactic antibiotics to prevent anal fistula development. There is a need for a study to establish whether adding antibiotic treatment to surgical drainage of perianal abscess results in a reduction in perianal fistulas.

Methods and analysis This multicentre, double-blind, randomised, placebo-controlled trial investigates whether addition of antibiotics (ciprofloxacin and metronidazole) to surgical drainage of a perianal abscess is beneficial compared with surgical drainage alone. The primary outcome is the development of a perianal fistula within 1 year. Secondary outcomes include quality of life, treatment costs, need for repeated drainage, patient-reported outcomes and other clinical outcomes. Participants are recruited in one academic and seven peripheral Dutch clinics. To demonstrate a reduction of perianal fistula from 30% to 15% when treated with adjuvant antibiotics with a two-sided alpha of 0.05, a power of 80% and taking a 10% loss to follow-up percentage into account, the total sample size will be 298 participants. Data will be analysed according to the intention-to-treat principle.

Ethics and dissemination The study protocol has been approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centers (nr. 2021_010). Written consent is obtained from each participant prior to randomisation into the study. The results of this trial will be submitted for publication in international peer-reviewed journals, presented at conferences and spread to coloproctological associations.

Trial registration numbers 2020-004449-35; NCT05385887.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Secondary endpoints include quality of life, proctology-specific patient-reported outcomes, financial costs, as well as clinical outcomes.
⇒ Study admissions will prove to be challenging because a perianal abscess generally demands rapid surgical treatment and thus a relatively short time window for patient inclusion.
⇒ The number of pills patients will have to take may prove to be challenging regarding patient compliance with the study protocol.
⇒ The primary endpoint will be determined by clinical evaluation and will not be objectively assessed through MRI.

INTRODUCTION

Perianal fistula is a burdening disease with an annual incidence of 6–12/100 000 people in Western countries.[1 2] Treatment is often difficult and in case of high complex fistula more than 50% of patients undergo more than two operations with still very variable results. In the Netherlands, every year, more than 5000 operations are carried out for perianal fistula.[3] Consequences for social and work life are considerable and therefore present an economic burden. More than 35% of crypto-glandular fistula originate from perianal abscess.[1] Despite adequate drainage of perianal abscess, up to 83% recur or result in a perianal fistula, the majority developing within the first 12 months.[4] Meticulous preoperative diagnosis and concomitant antibiotics are attempts to reduce this undesirable course, but evidence of its effect is scarce. There is some evidence that gut derived bacteria play a role in development of a perianal fistula.[5 6] Up till now, it is not common practice to routinely administer antibiotics. However, a relatively recent (2019) systematic review described a decrease of incidence of anal fistula development when surgical treatment of perianal abscess is accompanied by antibiotics.[7] Nevertheless, this review includes six studies of which most

have a retrospective nature and only two are randomised controlled trials. The randomised trial by Sözener *et al.* did not find a protective effect regarding the risk of fistula formation with amoxicillin-clavulanic acid.[8] The other randomised trial demonstrated positive effects of ciprofloxacin with metronidazole; however, this was a single centre and single blinded study.[9] International guidelines addressing treatment of perianal abscess recommend drainage and in case of immunosuppression or systemic illness addition of antibiotics, but level of evidence is low (2C).[10 11] The Dutch coloproctology guideline does not specifically address treatment of perianal abscess. Further high-quality studies are required to clarify the effect of antibiotic treatment in addition to drainage of perianal abscess. Reports of treatment costs and cost-effectiveness for patients with perianal fistula are scarce. Only one recent Swedish study investigated disease-associated costs and concluded that the burden on society is high which justifies all attempts to reduce occurrence.[12] Prevention by treating perianal abscess adequately would contribute to this attempt. A trial comparing efficiency of adequate drainage of perianal abscess followed by postoperative antibiotics versus drainage followed by placebo drugs is warranted.

Objectives

Primary objective

The primary objective of this trial is to establish whether adding antibiotic treatment to surgical drainage of perianal abscess results in less perianal fistula after 1 year.

Secondary objectives

The key secondary objectives are to determine whether adjuvant antibiotic treatment also leads to higher quality of life (QoL) at 12 months, and whether it leads to lower costs, less need of repeated drainage, better patient-reported outcomes (PROMs) and improvement of clinical outcomes (discharge from the hospital, complication rate, recurrent abscess within 1 year, duration of possible readmission in the hospital within 90 days).

Hypothesis

We hypothesize that treatment with adjuvant antibiotics following perianal abscess drainage will diminish the development of perianal fistula.

METHODS AND ANALYSIS

Study design

The ATLAS (Antibiotic Treatment foLlowing surgical drAinage of perianal abscess) trial concerns a multicentre, double-blind, placebo-controlled, randomised trial with treatment of perianal abscess by surgical drainage alone or in combination with antibiotics. The trial was registered at EudraCT and ClinicalTrials.gov. The protocol was drafted in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statements.[13] Patients will be accrued by all eight participating Dutch clinics. The first participant was recruited on 23 December 2021. At the time of submission of this manuscript all eight clinics are in the recruiting phase, which will contain 18 months, after which a follow-up period of 12 months is scheduled. The design involves allocation of all appropriate consecutive patients with a primary occurrence of perianal abscess to surgical drainage followed by either antibiotics or placebo. After eligibility has been established and patients have given written informed consent, patient details will be collected, and patients will be randomised to either one of the treatment arms. Data will be analysed on 'intention-to-treat' basis in case patients are not subjected to the randomised treatment modality.

Eligibility criteria

Inclusion criteria

- Age 18 years or older
- Eligible for email questionnaires
- Sufficient understanding of the Dutch written language (reading and writing)
- First episode of a perianal abscess

Exclusion criteria

- A coexistent anorectal fistula
- Secondary or recurrent perianal abscess
- Presence of an internal fistula opening
- Any additional surgical procedure performed during the same session
- Previous (peri)anal surgery
- Inflammatory bowel disease
- History of radiation of the pelvic area
- Anorectal malignancy
- Immunodeficiency or immunosuppressive medication at the time of surgery
- Valvular heart disease
- Pregnancy or lactation
- Acute or chronic kidney failure (eGFR<30 mL/min)
- Postoperative antibiotic prophylaxis indicated for another reason
- Allergy to either metronidazole or ciprofloxacin
- Not able or trouble with swallowing pills
- Concomitant use of:
  - Tizanidine, theophylline, clozapine, olanzapine, pirfenidone, carbamazepine, agomelatine (these are all CYP1A2 substrates, ciprofloxacin is an inhibitor)
  - Amiodarone, erythromycin, sotalol, azithromycin, citalopram, escitalopram, flecainide, fluconazole, haloperidol >5 mg/day, methadone, ondansetron (concerning prolonged QT interval in combination with ciprofloxacin)
  - Lithium (can cause toxic levels together with metronidazole)
  - Lopinavir/ritonavir, ritonavir capsules, temsirolimus, disulfiram (Antabuse), mebendazole (can cause serious side effects, confusion and psychosis in combination with metronidazole)

  - Corticosteroids (gives a higher risk at tendinitis and tendon rupture together with ciprofloxacin)
- Not able or willing to provide written informed consent

Interventions

The antibiotic group receives 7 days of oral metronidazole (500 mg every 8 hours) and ciprofloxacin (500 mg every 12 hours) in addition to surgical drainage. Mixed enteric flora was found at the site of surgery in patients who developed a fistula after abscess drainage. This combination of antibiotics covers gram positive/negative bacteria (ciprofloxacin) and anaerobic bacteria (metronidazole), giving a complete coverage of the bacterial spectrum.[14] Patients allocated to the placebo group will receive placebo medication in a similar form following surgical drainage.

The antibiotics are purchased as generic tablets from a commercial supplier. The labelling of the medication will be done in the Trial Pharmacy of the AUMC, location AMC. The medication is packaged in two identical vials for blinding purposes.

We chose to conduct a pragmatic study that mimics the current daily practice in the Netherlands best. Therefore we chose not to standardise the surgical procedure but leave this up to the surgeon. In general, the surgical drainage is performed by either a colorectal surgeon or resident under general or local anaesthesia. The patient is placed in lithotomy position and the rectum is first examined. The abscess is incised and adequately drained. The abscess cavity is debrided. The rectum is checked for an internal opening or presence of proctitis. The wound is left open for secondary healing. When possible preoperative or perioperative diagnostics will be done by either (endo-) ultrasonography or MRI.

Outcomes

Primary outcome

Primary study endpoint is the development of a perianal fistula within 12 months (dichotomous: yes/no). A perianal fistula is diagnosed based on findings from physical examination. When patients do not attend their appointment they will receive a telephone call after 12 months where the doctor asks for symptoms as serosanguineous discharge and pain. An external opening with or without serosanguineous discharge is considered a fistula. In case of doubt, an endo-anal ultrasonography or MRI scan is performed.

Secondary outcomes

Secondary study endpoints include QoL at 12 months and several financial and functional outcomes for which multiple questionnaires at different time points will be used during the follow-up period (table 1). These questionnaires are sent to patients by email with access to a web-based tool (Castor^{SMS}). If patients do not have email accounts, the questionnaires will be sent to their home address by envelope. In case of unreturned forms, participants are contacted by email or telephone to obtain the missing data.

QoL is measured with the 5-level EQ-5D version (EQ-5D-5L) questionnaire with Dutch rating, a generic Health Related Quality of Life (HRQoL) tool which is broadly used in economic evaluations. It consists of a 5-item EQ-5D descriptive system and the EQ-Visual

Table 1 Participant timeline

	Study period				
	Enrolment/allocation	Postallocation			
Time point	Baseline	1 week	3 months	6 months	12 months
Eligibility screen	X				
Informed consent	X				
Surgical drainage	X				
Allocation	X				
Perioperative data/clinical outcome measures	X	X			
Return of medication flasks to the pharmacy		X			
Visit outpatient clinic with physical examination*		X			X
Questionnaires					
EQ-5D-5L	X	X	X	X	X
iPCQ		X	X	X	X
iMCQ		X	X	X	X
proctoPROM	X	X	X	X	X

*1 week and 12 months after drainage are two mandatory visits to the outpatient clinic. In between data will be collected if an unscheduled appointment is required.
EQ-5D-5L, 5-level EQ-5D version; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost Questionnaire; proctoPROM, proctology patient-reported outcome measurement.

Analogue Scale (EQ-VAS). The first comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and responses result in a patient's health state that can be transformed into an HRQoL index score ranging between 0 (death) and 1 (full health). These index scores are combined with the length of life to calculate the cost per quality adjusted life year (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.

Patient-reported complaint reduction is evaluated with the proctology PROM, a recently validated proctology specific patient-related outcome measurement.[15] Clinical outcome measures that will be analysed are the need of repeated drainage, recurrence of perianal abscess within 1 year, surgical procedure data (ie, level of expertise of the surgeon/resident, type of surgery performed, blood loss in millilitres, 'skin-to-skin' operation time, intraoperative complications), reason and duration of possible hospital readmissions within 90 days postoperatively, day of discharge from the hospital, duration of absence from work and surgery-related complications (postoperative bleeding, urinary retention requiring catheterisation, emergency reoperation, anal stenosis and faecal incontinence) using the Clavien-Dindo classification.[16] In case of repeated drainage of recurrent perianal abscess, and an underlying fistula is objectified, both recurrence and fistula are scored.

Also, total costs will be assessed by summing the in-hospital direct and indirect costs, out-of-hospital postoperative costs, which will be measured with the iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ), and the costs related to recurrence, reintervention, morbidity and productivity loss because of loss of workdays.

Participant timeline

The study period starts from the moment of providing written informed consent and continues until 12 months after surgery. One or two weeks after surgery patients will have an appointment at the outpatient clinic for routine check-up after surgery. During that visit the flasks in which the study medication is distributed must be returned to the local pharmacies to register therapy compliance. The amount of medication that is returned will be accounted by trained personnel of the local pharmacies. These pharmacy employees are unblinded but are independent of the study group and study outcomes. Study medication that is returned will be destroyed at the local pharmacy of the participating centres.

In the following months the questionnaires are sent by email as is presented in table 1. At 12 months postsurgery an extra appointment at the outpatient clinic is scheduled to determine whether a fistula has developed.

Sample size calculation

Fistula rate formation after surgical drainage of a perianal abscess varies from 30% to 48% without use of antibiotics.[8 9 17 18] In the available literature, an incidence of 14%–22% is described for patients receiving postoperative antibiotics.[7] Considering these available data an expected reduction of 15% assuming an incidence of 30% in the group receiving placebo seems appropriate. To demonstrate a reduction of perianal fistula from 30% to 15% when treated by adjuvant antibiotics with a two-sided alpha of 5% and a power of 80%, a total of 134 patients in each group is required. Taking a 10% loss to follow-up percentage into account, a total of 298 patients is necessary to be included in our study.

Patient and public involvement

We have included the patient organisation Bekken4all in the preparation of this protocol. They played an important role in providing information about importance for patients suffering from perianal abscess or fistula but also making sure the study load for the participants was not overlooked. During the course of this study, they will be included in several meetings to give their patients' perspective on study results and implementation plans.

Recruitment

In most cases, patients will be screened for eligibility in the emergency department or outpatient clinic by the consultant or surgical resident and this will be noted in a trial logbook. Like in normal clinical practice, the patient will be informed about the procedure of abscess drainage. Then the physician will explain the study and give each eligible patient written information by means of the Patient Information Sheet. This explains the rationale behind the study, as well as what taking part encompasses. The local researcher checks the patient's medication list for drug interactions with the study medication and gives advice when necessary (eg, extra INR check when the patient uses vitamin K antagonists or an extra blood glucose test when oral diabetic agents are used).

Allocation/randomisation/blinding

After fully signed written informed consent, patients will be randomly allocated to postoperative antibiotics or placebo drugs following surgical drainage. Randomisation is performed by a web-based tool (Castor^{SMS}) and assignment to one of the two groups is blinded for both the participant and the surgeon (double-blind). The randomisation sequence is computer generated, with 1:1 allocation ratio to either group and generating a unique record number. The local pharmacy receives the randomisation email with the unique record number and allocated treatment. The local pharmacy removes the flag labels from the Investigational Medicinal Product (IMP) and dispenses the trial medication. The list with included patients and given study medication will be available at the pharmacy. The local treating physician can contact the local pharmacy when unblinding is necessary. This can only be done in two cases: (1) if the surgeon decides to treat with antibiotics for another reason after randomisation took place, (2) if a patient is suspected of having side

effects that might be due to metronidazole or ciprofloxacin. The research team will be notified that the patient is unblinded and will be excluded from receiving any study medication. However, the patient's allocation arm remains unknown to the research team. Until the primary analysis is completed all physicians and researchers will remain blinded to treatment allocation.

Data collection

Each participating centre's personnel involved in treating patients with perianal abscess are trained in providing eligible patients with both oral and written information about the procedure of surgical drainage and the importance and possible benefits of our study. All the medical baseline and perioperative data are collected at the individual hospitals. These data are recorded in standardised case record forms (CRFs) in Castor. The procedure of surgical drainage and postoperative instructions are standardised and similar to normal Dutch clinical practice. Postoperative parameters, complications and physical examination during routine follow-up are assessed by competent surgical residents or surgeons and are also recorded in the CRF. The study medication is handed out to the participants by trained pharmacy personnel together with an organised scheme for patients to cross off the medication that they have taken. This will help them follow the study protocol and help them remember to take the medication (five pills per day for 7 days). Furthermore, at the 1-2 week follow-up visit the surgeon will examine these schemes to determine therapy compliance.

Validated questionnaires follow a vast schedule (table 1). Patients are approached by the study group via email or telephone if they fail to complete them within 1 week. There is a 1 moth time limit set to complete the questionnaires at 3, 6 and 12 months. The appointment at the outpatient clinic 1 year after surgery is scheduled with the local investigator of the participating centre to ensure correct evaluation of the primary endpoint. Participants will be financially compensated for extra travel costs.

Statistical analysis

Data will be analysed according to the intention-to-treat principle. Analyses will be carried out using SPSS V.26.0. A p value of <0.05 will be considered a threshold for significance. The primary outcome of the study: the difference in number of perianal fistulas between the two groups within 12 months will be tested with the χ^2 test or Fisher exact test. Descriptive methods will be used to check the quality of the data, homogeneity of the two treatment groups and primary and secondary endpoints. Histograms will be used to analyse the normality of the data.

Differences in QALYs and other PROMs will be calculated with linear interpolation between successive time points and presented together with their 95% Confidence Intervals (CIs). Other secondary outcomes will be analysed using either a t-test or Mann-Whitney U test for continuous data and a χ^2 test or Fisher exact test for categorical data. Differences will be reported with 95% CIs. If missing data exceeds 10% of the data, and if these missing data are at random, then 10 imputed datasets will be generated using multiple imputations with predictive mean matching. The analysis will be performed on the 10 imputed sets and combined using Rubin's rules.

Cost-effectiveness analyses

We hypothesize that drainage of the perianal abscess together with antibiotic treatment compared with drainage alone will result in fewer patients with a perianal fistula and therefore a better QoL. We will perform a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). The primary outcome in the CEA will be the cost per prevented perianal fistula. The primary outcome in the CUA will be cost per QALY, which can provide evidence to change guidelines and help modify healthcare policies. Both analyses will be performed from a societal perspective with a time horizon of 12 months. Furthermore, a lifelong evaluation of the cost differences will be assessed using Monte Carlo simulations. To account for uncertainties a probabilistic sensitivity analysis will be performed.

Incremental cost-effectiveness ratios will be calculated as the difference in costs per prevented fistula and per QALY. Sampling variability in the CEA and 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 cost-effectiveness acceptability curves. Sensitivity analyses will be done for the unit costs of healthcare.

Cost analysis

The most recent guidelines for costing in healthcare research will be followed which includes both medical and patients costs as also productivity losses.[19] The medical costs cover all the costs made for perianal abscess treatment and treatment of all complications, including perianal fistula. Patient costs include personal expenses like over-the-counter medication and healthcare related travel costs. Not being able to go to work and decreased productivity during work contribute to productivity losses and thus to indirect extra non-medical costs.

Hospital healthcare usage will be retrieved from hospital information systems and CRFs. Data on out-of-hospital healthcare and productivity losses will collected with the iMCQ and iPCQ. Questions on personal expenses are added to these questionnaires. Participants are asked to fill in these questionnaires at various time points. Furthermore, these 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. In the lifelong evaluation a discounting of costs and effects will be done to account for time preferences.

Patient outcome analysis

The EQ-5D-5L questionnaires will be used to estimate the differences in QoL between the two groups. These scoring indexes can be converted into a health utility score based on tariffs from the general Dutch population.[20] Then, using linear interpolation between the successive health utility assessment over time, QALYs can be calculated for each patient. Number of fistulas per treatment group will be recorded from the hospital data.

Budget impact analyses

Following the ISPOR guidelines, we will assess the costs of perianal abscess drainage together with antibiotics from both governmental and hospital perspectives.[21 22] The first can contribute to making changes in healthcare strategies. The latter can be used to examine the financial consequences for the individual hospitals. The budget impact study will be based on incidence and prevalence figures and thus will reflect the net savings of less perianal fistulas resulting from the use of antibiotics. The time horizon of the budget impact will be 5 years and reported for each successive calendar year.

Different implementation scenarios of antibiotic treatment will be assessed: immediate, gradual (25% increase of implementation per year during the first 4 years) or partly (70%, 80% and 90%). Sensitivity analyses will be performed for the size of the target population over time, the observed uncertainty of antibiotic medication in reducing the amount of perianal fistula.

Cost analysis

The budget impact analysis from the governmental societal perspective will follow the most recent guideline.[19] Impact assessments concerning premium financed healthcare and from the hospital perspective will use existing prices at the time of analysis (DBC costs). Sensitivity analysis in implementation scenarios and medical costs will be performed.

Diversity

No patient will be excluded based on gender or cultural background. We will, post hoc, 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 are not expected.

ETHICS AND DISSEMINATION

Ethics approval

This trial will be carried out according to the principles of the Declaration of Helsinki (Fortaleza October 2013) and in accordance with the WMO and other European guidelines, regulations and acts such as the General Data Protection Regulation. The Medical Ethics Committee of the Amsterdam University Medical Centers, location Academic Medical Center has approved the study protocol (nr. 2021_010).

Consent procedure

Eligible patients will receive written information and are informed in person by the treating surgeon or authorised surrogates who are aware of the trial details. Informed consent should be obtained from each patient according to the guidelines of the local ethical committee, prior to randomisation into the study. The information offered to the patient or legal representative contains several important aspects (online supplemental appendix A): it is made clear the trial involves research and a full explanation of the procedures, nature, expected duration and purpose of the study is given. Also, all possible foreseeable risks of harms and possible benefits that may be expected are disclosed to the patient. Patient data must be handled with care and confidentiality, and data is saved for 15 years. Participation is voluntary and the patient may discontinue participation at any time and remain free to withdraw without giving reason, in which case the patient will receive standard treatment (no standard antibiotics). Finally, legally incompetent adults and minors are excluded from the trial.

Risk of harms

Monitoring of the trial will be conducted by the Clinical Monitoring Center (CMC) of the Amsterdam UMC. The CMC is independent from the study and study team and has access to the data and source documents of the trial. They have predesigned a monitoring plan in which site evaluation visits are scheduled to review the quality of the participating sites and one thorough risk assessment is performed.

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety, as is in accordance with the WMO. The sponsor will notify the accredited Medical Ethical Committee (MEC) 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 MEC. The investigator will take care that all subjects are kept informed. Also, the sponsor will report all serious adverse events and suspected unexpected serious adverse reactions to the accredited medical ethical committee. In addition, once a year throughout the clinical trial, the study group will submit a safety report to the accredited MEC and competent authority.

In accordance with article 7 of the WMO, the sponsor has a liability insurance, which covers the damage to participants through injury or death caused by taking part in our study and extends until 4 years after our study is finished.

Dissemination of results

The initiation and start of the study are made knowledgeable at the website of the Society of coloproctology in the Netherlands (Werkgroep coloproctologie; WCP). The trial contributes to evidence-based medicine and the results should become available for routine daily practice. The implementation activities comprise dissemination

activities and adoption of professional guidelines. The existing clinical guideline proctology may be adjusted: recommendations following from this study will be summarised in this guideline. The guideline is available to clinicians, patients, insurance companies and other healthcare providers. The result of implementation of the proposed study can be measured using the existing registration system: the DBC Information System (DIS). 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 meetings of the Society of Coloproctology and at the annual meeting of the Dutch Society of Surgeons (Nederlandse Vereniging voor Heelkunde; NVvH). The NVMM (Dutch Society of Medical Microbiology) will also be informed about our results. It is expected that there will be sufficient support to update the Coloproctology guideline concerning the treatment of perianal abscess and fistulas. Resistance against results is expected to 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. We expect that this study provides sufficient data to produce several manuscripts for publication in respected peer-reviewed journals. Also, a summary of the results will be published on the Sponsor's website.

Public disclosure and publication policy

The presentations and publications that will derive from the data collected through this trial will be in the name of the study group. Future manuscripts answering new research questions may have individual authorships. 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 all patients has been completed.

Collaborators The ATLAS trial project group consists of: the principal investigators dr IJMH-G, surgeon Proctos Kliniek and prof dr WAB, surgeon and head of Surgery Amsterdam UMC location AMC; Coordinating investigators: JYvO and LD. The ATLAS trial steering committee consists of: IJMH-G, WAB, dr FHW Jonker, surgeon Rode Kruis ziekenhuis, dr O van Ruler, surgeon Ijsselland ziekenhuis, dr AHW Schiphorst, surgeon Diakonessenhuis, dr R Schouten, surgeon Flevoziekenhuis, dr RM Smeenk, surgeon Albert Schweitzer Ziekenhuis, dr DDE Zimmerman, surgeon Elisabeth-TweeSteden Ziekenhuis and dr S van Dieren, epidemiologist/statistician Department of Surgery Amsterdam UMC location AMC.

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

Funding The study is supported by The Netherlands Organization for Health Research and Development (ZonMw), grant number 80-86600-98-19047. Trial sponsor: Proctos Kliniek, professor Bronkhorstlaan 10, 3723 MB Bilthoven, The Netherlands.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Justin Y van Oostendorp http://orcid.org/0000-0002-2835-3997
Lisette Dekker http://orcid.org/0000-0001-8092-7196

REFERENCES

1 Sainio P. Fistula-In-Ano in a defined population. incidence and epidemiological aspects. *Ann Chir Gynaecol* 1984;73:219–24.
2 Nelson R. Anorectal abscess fistula: what do we know? *Surg Clin North Am* 2002;82:1139–51. v-vi.
3 Open dis data. Available: https://www.opendisdata.nl/
4 Oliver I, Lacueva FJ, Pérez Vicente F, *et al*. Randomized clinical trial comparing simple drainage of anorectal abscess with and without fistula track treatment. *Int J Colorectal Dis* 2003;18:107–10.
5 Hamadani A, Haigh PI, Liu I-LA, *et al*. Who is at risk for developing chronic anal fistula or recurrent anal sepsis after initial perianal abscess? *Dis Colon Rectum* 2009;52:217–21.
6 Fielding MA, Berry AR. Management of perianal sepsis in a district general Hospital. *J R Coll Surg Edinb* 1992;37:232–4.
7 Mocanu V, Dang JT, Ladak F, *et al*. Antibiotic use in prevention of anal fistulas following incision and drainage of anorectal abscesses: a systematic review and meta-analysis. *Am J Surg* 2019;217:910–7.
8 Sözener U, Gedik E, Kessaf Aslar A, *et al*. Does adjuvant antibiotic treatment after drainage of anorectal abscess prevent development of anal fistulas? A randomized, placebo-controlled, double-blind, multicenter study. *Dis Colon Rectum* 2011;54:923–9.
9 Ghahramani L, Minaie MR, Arasteh P, *et al*. Antibiotic therapy for prevention of fistula in-ano after incision and drainage of simple perianal abscess: a randomized single blind clinical trial. *Surgery* 2017;162:1017–25.
10 Vogel JD, Johnson EK, Morris AM, *et al*. Clinical practice guideline for the management of anorectal abscess, fistula-in-ano, and rectovaginal fistula. *Dis Colon Rectum* 2016;59:1117–33.
11 Ommer A, Herold A, Berg E, *et al*. German S3 guidelines: anal abscess and fistula (second revised version). *Langenbecks Arch Surg* 2017;402:191–201.
12 Lundqvist A, Ahlberg I, Hjalte F, *et al*. Direct and indirect costs for anal fistula in Sweden. *Int J Surg* 2016;35:129–33.
13 Chan A-W, Tetzlaff JM, Altman DG, *et al*. Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
14 Whiting JL, Cheng N, Chow AW. Interactions of ciprofloxacin with clindamycin, metronidazole, cefoxitin, cefotaxime, and mezlocillin against gram-positive and gram-negative anaerobic bacteria. *Antimicrob Agents Chemother* 1987;31:1379–82.
15 Vander Mijnsbrugge GJ, Molenaar C, Buyl R, *et al*. How is your proctology patient really doing? Outcome measurement in proctology: development, design and validation study of the Proctoprom. *Tech Coloproctol* 2020;24:291–300.
16 Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.

17 Hämäläinen KP, Sainio AP. Incidence of fistulas after drainage of acute anorectal abscesses. *Dis Colon Rectum* 1998;41:1357–61.
18 Lohsiriwat V, Yodying H, Lohsiriwat D. Incidence and factors influencing the development of fistula-in-ano after incision and drainage of perianal abscesses. *J Med Assoc Thai* 2010;93:61–5.
19 Hakkaart-van Roijen L, Essink-Bot M-L. *Manual health and labour questionnaire*. Institute for Medical Technology Assessment (iMTA), 2000.
20 M Versteegh M, M Vermeulen K, M A A Evers S, *et al*. Dutch tariff for the five-level version of EQ-5D. *Value Health* 2016;19:343–52.
21 Sullivan SD, Mauskopf JA, Augustovski F, *et al*. Budget impact analysis-principles of good practice: report of the ISPOR 2012 budget impact analysis good practice II Task force. *Value Health* 2014;17:5–14.
22 Goettsch WG, Enzing J. Review: report of the ISPOR 2012 budget impact analysis good practice II Task force. *Value Health* 2014;17:1–2.