Optimising diagnostics to discriminate complicated from uncomplicated appendicitis: a prospective cohort study protocol

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ABSTRACT

Introduction Growing evidence is showing that complicated and uncomplicated appendicitis are two different entities that may be treated differently. A correct diagnosis of the type of appendicitis is therefore essential. The Scoring system of Appendicitis Severity (SAS) combines clinical, laboratory and imaging findings. The SAS rules out complicated appendicitis in 95% (negative predictive value, NPV) and detects 95% (sensitivity) of patients with complicated appendicitis in adults suspected of acute appendicitis. However, this scoring system has not yet been validated externally. In this study, we aim to provide a prospective external validation of the SAS in a new cohort of patients with clinical suspicion of appendicitis. We will optimise the score when necessary.

Methods and analysis The SAS will be validated in 795 consecutive adult patients diagnosed with acute appendicitis confirmed by imaging. Data will be collected prospectively in multiple centres. The predicted diagnosis based on the SAS score will be compared with the combined surgical and histological diagnosis. Diagnostic accuracy for ruling out complicated appendicitis will be calculated. If the SAS does not reach a sensitivity and NPV of 95% in its present form, the score will be optimised. After optimisation, a second external validation will be performed in a new group of 328 patients. Furthermore, the diagnostic accuracy of the clinical perspective of the treating physician for differentiation between uncomplicated and complicated appendicitis and the patient’s preferences for different treatment options will be assessed.

Ethics and dissemination Ethical approval was granted by the Amsterdam UMC Medical Ethics Committee (reference W19_416 # 19.483). Because of the observational nature of this study, the study does not fall under the scope of the Medical Research Involving Human Subjects Act. Results will be presented in peer-reviewed journals. This protocol is submitted for publication before analysis of the results.

INTRODUCTION

Background Acute appendicitis is one of the most common abdominal infectious diseases.1 2 It was a long-held belief that every uncomplicated appendicitis would ultimately progress into a complicated (gangrenous or perforated) appendicitis, with an associated increase in morbidity. For this reason, appendectomy has been the standard treatment of acute appendicitis since it was invented in 1886.3–5 However, growing evidence shows that complicated and uncomplicated appendicitis are two different entities.6–9

The two different entities of appendicitis may be treated differently. Patients with complicated appendicitis could benefit from timely surgery. The unpublished secondary analysis of a Dutch prospective cohort study,10 consisting of 1975 patients who had been operated on for suspected acute appendicitis, showed that patients with complicated appendicitis who are operated within 8 hours after presentation have fewer postoperative complications than patients with an in-hospital delay of more than 8 hours. In contrast to patients with complicated appendicitis, surgery for uncomplicated appendicitis can be delayed safely up to 24 hours without increasing the...
risk of morbidity or postoperative complications. Moreover, an increasing number of studies showed that treating uncomplicated appendicitis with antibiotics might be a safe, effective and cost-saving alternative for appendectomy. Some studies even suggest that uncomplicated appendicitis can be treated by supportive treatment without antibiotics. For these different treatment options, a correct diagnosis is essential.

Current diagnostic strategies have insufficient discriminatory accuracy to correctly differentiate complicated from uncomplicated appendicitis. Although imaging modalities are good to excellent for the diagnosis of acute appendicitis in general, the ability to distinguish between complicated and uncomplicated appendicitis is inadequate. This shortcoming is highlighted by a meta-analysis of RCTs on the antibiotic treatment of uncomplicated appendicitis. Although all trials intended to include only patients with uncomplicated appendicitis, 16.9% of patients randomised to surgery were found to have complicated appendicitis. Better identification of patients with complicated appendicitis is needed to discover the actual merits of antibiotic treatment.

The Scoring system of Appendicitis Severity (SAS) has been developed for this differentiation. The SAS combines clinical parameters and imaging features. Two variants of the SAS were developed: SAS-US and SAS-CT, see Table 1. Using a cut-off score of five points or less for the SAS-US and six points or less for the SAS-CT, the scores reach sensitivities of 96.6% and 90.2% and negative predictive values (NPVs) of 97.1% and 94.7% for complicated appendicitis, respectively. Average sensitivity and NPV are around 95% when the ratio of patients diagnosed by ultrasound (US) and CT is considered. This ratio was 68.2/31.8, according to national SNAPSHOT data from the Netherlands. Based on this accuracy, the SAS would be sufficient in ruling out complicated appendicitis. However, the SAS has not yet been validated externally in a well-designed prospective study. This is one of the main reasons why the SAS is not currently used in clinical practice. When non-surgical treatment of appendicitis will become a more frequently used treatment option and not all patients undergo appendectomy, a reliable tool to distinguish between uncomplicated and complicated appendicitis becomes crucial.

If patients with complicated appendicitis can be identified reliably, for example, using the SAS, antibiotic treatment may become a standard alternative for surgery. In selecting the right treatment option, it is important to acknowledge the patient’s preferences for non-operative or operative treatment. Few studies have described the patient’s choice for treatment of uncomplicated appendicitis, and a wide range of patients preferring non-operative treatment has been reported, varying from 9.4% to 57%. This wide range may be explained by the different ways of informing the participants and by the type of the included patients. To facilitate shared decision making for uncomplicated appendicitis, the correct group of participants should be surveyed, and accurate information must be provided about the risks and advantages of both antibiotic and surgical treatment.

### Study objectives

This study aims to validate the SAS in adults suspected of acute appendicitis externally. Validation will be completed if the target 95% sensitivity and 95% NPV are reached (scenario A). If the validation of the SAS does not match these targets, optimisation of the SAS will be performed (scenario B). In this scenario, inclusions will continue to create a new validation cohort. Optimisation and validation of the modified score will be secondary objectives. A secondary aim of this study is to evaluate the preference for antibiotic or surgical treatment of uncomplicated appendicitis in adult patients who had undergone an appendectomy.

### METHODS

#### Overall study design

A multicentre, prospective, observational study will be conducted in Dutch teaching and non-teaching hospitals. Diagnostic work-up will be performed according to the current standards (Dutch guidelines). The Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 guidelines are used.

#### Study population

Consecutive adult patients will be included at the emergency department (ED). Inclusion started at the first hospital on 26 January 2020, was subsequently hampered by the COVID-19 pandemic and was then expanded to multiple hospitals. Inclusion will continue until the

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**Table 1** Scores and features from SAS-US and SAS-CT

| Feature                        | SAS-US | SAS-CT |
|-------------------------------|--------|--------|
| Age ≥45 years                 | 2      | 2      |
| Temperature                   |        |        |
| ≤37.0                         | 0      | 0      |
| 37.1–37.9                     | 2      | 2      |
| ≥38.0                         | 4      | 4      |
| Duration of symptoms ≥48 hours| 2      | 2      |
| WCC>13×10⁹ /L                 | 2      | 2      |
| CRP (mg/L)                    |        |        |
| ≤50                           | 0      | 0      |
| 51–100                        | 4      | 2      |
| >100                          | 5      | 3      |
| Presence on imaging           |        |        |
| Free air                      | –      | 5      |
| Periappendiculair fluid       | 2      | 2      |
| Appendicolith                  | 2      | 2      |

CRP, C reactive protein; SAS, Scoring system of Appendicitis Severity; WCC, white cell count.
Consecutive adult patients, clinically suspected of acute appendicitis

Imaging confirms diagnosis of acute appendicitis

Intention to perform an appendectomy

Inclusion if informed consent for data use is signed

Exclusion if:
- the patient is pregnant
- final treatment is other than surgery
- surgery takes place >48 hours after imaging
- surgery due to suspected neoplasm

Appendectomy, resulting in a surgical diagnosis (preferably followed by histology)

Figure 1  Flow chart of inclusion and exclusion.

The minimum number of required participants is reached. Inclusion takes place when the patient is diagnosed with acute appendicitis based on clinical, laboratory and imaging findings (see figure 1).

Inclusion criteria
To be included, patients must fulfill all of the following criteria:
- ≥18 years of age.
- Imaging-confirmed or—highly suspected diagnosis of acute appendicitis.
- Treatment by surgery with the intention to perform an appendectomy.

Exclusion criteria
Patients fulfilling one or more of the following criteria will be excluded:
- No surgery with the intention of appendectomy has been executed because a surgical specimen is needed as a reference standard.
- The surgery took place >48 hours after diagnosis based on the last performed imaging. It was considered that after 48 hours, the preoperative diagnostic results, and thereby the associated SAS score, are not representative of the intraoperative diagnosis.
- The patient is pregnant, as the SAS has been developed based on data in which pregnancy was an exclusion criterion.
- Patients who undergo surgery for suspected neoplasm as a cause of their appendicitis.

Data collection
All parameters will be collected prospectively. Data will be collected using standard reports as saved in the electronic health record (EHR). Data will be stored in an online database, namely CASTOR EDC (Electronic Data Capture). In addition to all prospectively scored variables, the final radiology, operation and histology reports will be collected for additional information.

Emergency department
The treating physician at the emergency department (ED) will complete a standardised report (see online supplemental, case report form (CRF) ED) that is saved in the EHR. The report consists of all parameters included in the SAS-score and other potentially predictive factors for complicated appendicitis, that is, smoking status, complaints of vomiting, and the numeric pain rating scale.26 We do not hand a scoring card to the treating physicians, nor will the final SAS score be shown in the acute setting.

Radiology report
Imaging results will be collected according to a standardised radiology report, including the following parameters: visualisation of the entire appendix, appendiceal diameter, presence of periappendiceal fat infiltration, presence of periappendiceal and/or intra-abdominal free fluid, presence of an appendicolith, presence of abscesses, including its diameter if present and destruction of the appendiceal wall (perforation). Destruction of the appendiceal wall is a discontinuity of the wall; a well-known finding and a sign used for diagnosing perforation.27–29 For CT and MRI, the presence of extraluminal air outside the appendix will be scored as well. Intra-abdominal free air cannot be reliably ruled out by US and is therefore not scored for this modality. For MRI, the presence of restricted diffusion will also be scored.30 31 This is an MRI-specific parameter that cannot be described using US or CT.

Clinical perspective
After diagnosing acute appendicitis, both the treating physician at the ED and the radiologist will be asked to differentiate between complicated or uncomplicated appendicitis. All available information can be used for this decision, including clinical, laboratory and imaging findings, augmented by their clinical experience. Information will be collected about the physician’s years of experience, their working department and the level of certainty for this differentiation, based on an 11-point Likert scale.

Surgery report
Intraoperative findings will be collected using standardised paper forms or similar standardised electronic reports (See online supplemental file 1, CRF Surgeon). Parameters that will be collected are the presence and aspect of intra-abdominal fluid, the need for postoperative antibiotic treatment, the occurrence of iatrogenic perforation and the intraoperative diagnosis. The surgeon chooses one of the following diagnoses: (1) normal appendix, (2) uncomplicated appendicitis, (3) gangrenous appendicitis, (4) perforated appendicitis, (5) acute appendicitis with a large infiltrate or (6) other, specify: …. Furthermore, the surgeon will take a picture.
of the appendix intra-abdominally before removing it and one of the specimen on a white background after removal. These pictures can be used for consensus in case of doubt of the final diagnosis.

Pathological report
Histological findings will be collected using a standardised report in the EHR, including inflammation, necrosis, a perforation and presence of a neoplasm. Transmural inflammation is defined by inflammation localised from mucosa up to and including the muscularis propria. Necrosis is present if any form of necrosis is seen, ranging from localised to transmural necrosis. If one of the above cannot be answered for some reason, an explanation can be given. In addition, complete histology reports will be collected. Other signs of uncomplicated appendicitis, such as ulceration of the mucosa, will be actively sought in cases without transmural inflammation.

Questionnaires
A standardised patient-reported outcome measure questionnaires will be disseminated after 3 months of follow-up to explore the patients’ thoughts about the surgical and antibiotic treatment of uncomplicated appendicitis. Based on a scenario of a patient with uncomplicated appendicitis, participants will be asked about their preferred treatment after outlining the advantages and risks of both options. For instance, in the patient preference questionnaire we mention a 1-year recurrence rate of acute appendicitis of 23%, as is described in a recent meta-analysis by Sallinen et al. Additionally, we ask them to substantiate their choice by checking a list of prespecified arguments. As a final question, patients will be asked which risk percentage of recurrence of appendicitis after 1 year they would accept in case of antibiotic treatment. The preferred treatment is not asked before start of treatment as all appendicitis patients still undergo surgery and non-surgical treatment of appendicitis is not a true preference option in our clinical setting. We have chosen to send the patient preference questionnaire only after treatment to avoid ambiguity about the upcoming treatment. All patients undergo surgery. Questionnaires will be distributed by email via CASTOR EDC in a web survey. These answers will be digitalised and stored within CASTOR EDC.

Data processing
Data will be collected from the EHR, paper CRF’s and, in case of the questionnaires, directly in CASTOR ECD. A local researcher will collect the data. The researcher will collect the data without calculating the final scores of the SAS. All data will be pseudonymised and stored in CASTOR EDC.

Outcomes
Index test: SAS score
Depending on the last performed imaging modality, the SAS-US or SAS-CT score will be calculated. Patients who undergo CT after negative or inconclusive ultrasound results will be scored using the SAS-CT. Table 1 describes the points given for both SAS variants. Patients will be classified as uncomplicated appendicitis (SAS-US ≤5 points or SAS-CT ≤6 points) or as complicated appendicitis (SAS-US >5 points or SAS-CT >6 points). This predicted diagnosis will be compared with the reference standard. The predicted SAS-US and SAS-CT diagnoses will be merged into the overall SAS score of the total cohort.

Reference standard
The reference standard will be the final diagnosis based on the combination of surgical and histological findings. Uncomplicated appendicitis is defined as transmural inflammation or ulceration of the appendix or periappendix without evident signs of necrosis or perforation both microscopically and macroscopically. Complicated appendicitis is defined as transmural inflammation of the appendix with either clear signs of necrosis or gangrene as described by the pathologist, a perforation as described by the surgeon, or the presence of an intraperitoneal abscess or large periappendicular infiltrate as described by the surgeon. Since histological assessment is standard after appendectomy in the Netherlands, it is expected that both surgical and histological reports will be present in all patients. If there are cases without histological assessment, the surgical diagnosis will be used as the reference standard.

In mismatches between the final diagnoses of the surgeon and pathologist, the reference standard will be established by the consensus of an expert panel. This panel consists of two surgeons, two radiologists, one pathologist and one ED physician/surgical resident who will review a structured summary of clinical information during admission, operative notes, the pathology report, imaging findings and CRFs from the surgeon and pathologist. In case of disagreement among expert panel members, a final diagnosis will be assigned during a consensus meeting of the expert panel concerning the disagreement cases.

Patients with a final diagnosis other than uncomplicated or complicated appendicitis will be assigned to one of both groups for the primary analysis. Patients with a normal appendix and no other diagnosis in need of surgery are referred to as non-urgent patients. These patients will be assigned to the group of patients with uncomplicated appendicitis for the primary analysis. Patients with a diagnosis other than appendicitis but where surgery was needed are referred to as urgent patients. These patients will be assigned to the group of patients with complicated appendicitis for the primary analysis.

Primary outcomes
The primary endpoints are the sensitivity and NPV of the SAS for complicated appendicitis.

Secondary outcomes
The secondary outcomes are defined as: Specificity and PPV of complicated appendicitis.
Sensitivity analysis of patients with genuinely acute appendicitis. Sensitivity, specificity, NPV and PPV will be calculated for the SAS score in this subgroup.

Sensitivity, specificity, NPV and PPV for excluding complicated appendicitis will be calculated separately.

The discriminatory capacity of the SAS, SAS-US and SAS-CT by calculating the area under the curve.

The patient-reported preferred treatment (antibiotics vs appendectomy) in a case of uncomplicated appendicitis, according to the online questionnaire.

Sensitivity, specificity, NPV and PPV of the physician at ED and the radiologist in distinguishing complicated from uncomplicated appendicitis compared to SAS.

Data analysis

Primary outcomes

Contingency tables will be constructed, including the SAS score and the reference standard. The sensitivity and NPV of SAS for complicated appendicitis will be calculated. The 95%-CI and 97.5% one-sided CI for the lower limit will be calculated using the Wald statistic.

Secondary outcomes

Specificity and PPV will be calculated using the SAS score. Furthermore, contingency tables will be constructed for both the SAS-US and SAS-CT separately. Sensitivity, specificity, PPV and NPV will be calculated. The area under the curve of the SAS will be plotted and calculated in a receiver operating characteristic (ROC) curve. A similar analysis will be performed for the SAS-US and SAS-CT separately.

Sensitivity analysis will be performed, including only patients with truly acute appendicitis. Initially, included patients with a final diagnosis other than acute appendicitis will be excluded for this analysis. Sensitivity, specificity, NPV and PPV will be calculated for the SAS score in this subgroup.

Questionnaires will be analysed. The proportion of patients choosing antibiotic treatment, surgery or patients without a preference will be reported. The most important arguments for this choice and the 1-year recurrence risk of appendicitis patients are willing to accept if treated by antibiotics will be presented.

The diagnostic accuracy of the physician at the ED and the radiologist in distinguishing complicated from uncomplicated appendicitis will be calculated in terms of sensitivity, specificity, NPV and PPV for both ‘tests’. This objective estimation will be compared to the results of the SAS. Stratification will be made using the level of certainty of the specific diagnosis. On an 11-point Likert scale (score 0-10), a score of 7 points or higher will be defined as ‘certain’, while a score of 6 points or less will be interpreted as ‘uncertain’. Patients with a ‘certain’ clinical diagnosis of uncomplicated appendicitis will be highlighted because in these patients’ antibiotic treatment may be an option in the future. The significance of the differences will be calculated by the chi-square test. All binomial 95% CI will be calculated by the Wilson score interval.33

Optimisation

It is hypothesised that the SAS reaches an NPV of at least 95% and a sensitivity of 95% for complicated appendicitis. A lower limit of 3 per cent as the only limit of the corresponding one-sided 97.5% CI will be considered the bare minimum. If the sensitivity or NPV point estimates are below 92%, the scoring system will be optimised. We will perform the optimisation of the SAS using data from the first cohort. For the optimisation, possible variables collected from the CRF’s and medical reports will be used. These variables are identified as known predictors of complicated appendicitis from the literature. The variables that are included in the SAS will be re-evaluated or rescaled. Additionally, all extra collected data (see data collection) will be added to a multivariable model to optimise the SAS.

Continuous variables will be categorised. An optimal cut-off score will be chosen by visually exploring the possible associations between the variables and the final diagnosis of complicated appendicitis using restricted cubic spline functions. ‘Knots’ in these smooth spline functions are tested as possible cut-offs for the categorisation. This way, new variables will be categorised, and continuous SAS variables may be rescaled.

A multivariable logistic regression model with the categorical predictors, including the parameters used in the SAS, will be constructed and reduced with supervised backward selection. In general, parameters with a p value above 0.15 will be excluded stepwise. However, supervised backward selection allows that parameters expected to be of diagnostic value based on literature data and etiology remain included to facilitate future studies. The model will be transformed into a clinically applicable scoring system, multiplying the adjusted coefficient of each parameter and rounding it to the nearest integer. Total scores for every patient will be calculated. A cut-off analysis will be performed using the ROC curve to select patients with predicted complicated appendicitis, not exceeding 5% of false negatives. In addition to this rounded score model, options for a computer-based algorithm will be explored. In this model, continuous data will be used without cut-offs only if this increases the diagnostic accuracy of the model.

Optimisation of the model will be performed for both US and CT. Diagnostic accuracy measures will be calculated, and the score will be validated. The second cohort of patients will be included for this validation of the modified SAS score (see the Sample size calculation section). Data from these patients will be collected in the same manner as in the initial validation period.

Missing data

Missing data analysis will be performed for missing parameters needed for the primary outcome, that is, SAS criteria, using the missing value analysis module in SPSS. Patients in whom more than 30% of these data points are missing will be excluded from the study. In the other
cases of missing less than 30% of the data, the data will be imputed. Multiple imputations by chained equations will be performed. The number of imputed datasets will be based on the percentage of missing data for each parameter required for the primary outcome with a minimum of 5 up to a maximum of 50 imputation sets. Missing data analysis will show which parameters to include in the imputation model. Sensitivity analysis will be performed to show any differences between the initial data and the data including imputations.

In the case of optimisation, eligible parameters will be examined. Only parameters present in at least 60% of all patients will be included in the analysis. If necessary, these variables will be imputed as described above. The percentage of missing data and imputed parameters will be described.

**Sample size calculation**

**Validation period**

The targeted sensitivity and NPV for complicated appendicitis are both 95%. A lower margin of 3 per cent will be considered as the only limit of the corresponding one-sided 97.5% CI the bare minimum. When the number of complicated appendicitis equals 228, the one-sided 97.5% adjusted Wald CI will extend 3% from the observed percentage for an expected percentage of at least 95% for sensitivity. Given a prevalence of 28.7% complicated cases in the target population,10 about 795 patients need to be included initially to reach a minimum of 228 patients with complicated appendicitis among all included appendicitis.

With the same extent of 3% from the observed percentage for an expected percentage of at least 95% for NPV, a total of 228 patients of which the SAS score predicts uncomplicated appendicitis is needed. The SAS-US predicted uncomplicated appendicitis in 33.7% within the original cohort; for the SAS-CT, this was 52.8%.21 Within the target population, 66.1% is expected to be diagnosed based on US and 30.6% based on CT, initially or secondary to US.10 Patients with a diagnosis based on MRI or without imaging will be excluded for the validation. This results in predicted uncomplicated appendicitis for the combined SAS of 38.4% in all patients. Based on the previous SAS results, 594 patients need to be included.

To report both reliable sensitivity and reliable NPV, we need to include the highest number of those two. After including at least 228 patients with complicated appendicitis to achieve the target sensitivity and at least 228 patients with a SAS score predicting uncomplicated appendicitis to accomplish the target NPV, we will test our hypothesis and validate the SAS. The expected required number of patients is 795 for this validation cohort. The sample size has been adjusted to achieve a better precision of estimating $p$ and achieve that the interval includes $p$ close to $1-\alpha$ of the time. Also, the adjusted Wald CI will not be symmetrical, and thus its upper limit will not cross 1, contrary to the unadjusted Wald CI, based on the normal distribution.35

**Optimisation period**

If the validation does exceed the margin of 3% of the adjusted Wald statistics of the sensitivity or NPV, optimisation of the SAS will be executed. Optimisation will be performed by using the data of the 795 patients. To externally validate the optimised SAS, we need a new cohort of patients. We will include these patients after having the primary 795 patients. We again intend to achieve a sensitivity of 95%, now with a lower limit of 5% as the only limit of the corresponding one-sided 97.5% CI as the bare minimum. Because of the large cohort in which the SAS will be optimised, we consider a lower limit of 5% instead of 3% will suffice. We calculated that 328 patients are needed for this second validation cohort in case of the need for optimisation of SAS.

A maximum expected 1123 patients would be included. This total consists of the primary validation/optimisation cohort of 795 patients and, if needed, a second external validation cohort of 328 patients.

**Patient and public involvement**

No patients were involved in the development of the research question or the study design. As mentioned above, questionnaires will be sent to all participants to inquire about their treatment preferences. Patient input will be solicited in this way. All participants will be asked if they wish to be informed about the results of the study. Results will be communicated to these patients via email.

**ETHICS AND DISSEMINATION**

**Patient recruitment**

Patients will be recruited 24 hours a day. Informed consent will be obtained at the ED or the ward, both preoperatively and postoperatively. Information about the study will be given, and a medical doctor will answer questions before signing the informed consent. If a patient leaves the hospital before informed consent is obtained, informed consent will be accepted by letter or email. In consultation with our juridical department, this is in line with the design of this study. The study was declared to be not subject to the Medical Research Involving Human Subjects Act (WMO), as judged by the Medical Ethical Committee of the Amsterdam UMC, location AMC.

**Intervention and risk**

The SAS can be applied without adding diagnostics other than standard diagnostic workup protocols. It is a purely diagnostic study without direct management consequences for the included patients. Participants will receive diagnostics and treatment according to current standards, and there is no additional burden except for a single time point patient-reported outcome and preferences questionnaire. Participation will not result in any risks for the patients.
Compensation
No financial compensation will be provided. There is no indication of a travel allowance.

Patient privacy
Only relevant data will be collected from the electronic patient file, such as patient characteristics and primary and secondary outcomes specified as above. These data will be encrypted. The encrypted data will be stored in private storage, only available for involved researchers. The encryption code will be secured by a password and is only accessible for the (local) head researcher. The patient questionnaires will be anonymous and will only be marked by the study number. Pictures of the appendices intraoperatively will be collected too. The filing of these pictures with a unique study number will not be traceable to the patient. After pseudonymisation, all data will be collected in multiple centres and shared after encryption via the data collection programme CASTOR EDC. The data will be stored for 15 years. After this period, the data will be destroyed. When patients give their permission, the data can be used in other subject related studies for a more extended period. The collection of patient data will be reported to the local privacy officer. Collected data are open for reuse for research on the topic of appendicitis.

Publication and implementation
The results will be published in an international peer-reviewed journal. They will also be disseminated through international conferences, (inter)national guidelines and will be the base for further research and a change in practice. Data will be open for reuse after the publication of our results according to the FAIR principles.

After completion of the study, the national guideline can be adjusted according to the findings of this study. If the SAS shows to be accurate enough to rule out complicated appendicitis, non-surgical treatment is likely more effective than published results have shown to date. A new RCT comparing appendectomy to antibiotic treatment using this more accurate way to select uncomplicated appendicitis may be needed to see the real potential of non-surgical treatment of truly uncomplicated appendicitis.

If the SAS is implemented in the guidelines, it will be easier to stimulate its use. Pocket maps can be produced to disseminate the use of the SAS. Moreover, a web-based application or app could aid any doctor involved in diagnosing and treating patients with acute abdominal pain and the suspicion of acute appendicitis.

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