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Trials

STUDY PROTOCOL

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# SAME day amBulatory Appendectomy (SAMBA): a multicenter, prospective, randomized clinical trial protocol

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## Abstract

**Background** A recent meta-analysis concluded that outpatient appendectomy appears feasible and safe, but there is a lack of high-quality evidence and a randomized trial is needed. The aim of this trial is to demonstrate that outpatient appendectomy is non-inferior to conventional inpatient appendectomy in terms of overall morbi-mortality on the 30th postoperative day (D30).

**Methods** SAMBA is a prospective, randomized, controlled, multicenter non-inferiority trial. We will include 1400 patients admitted to 15 French hospitals between January 2023 and June 2025. Inclusion criteria are patients aged between 15 and 74 years presenting acute uncomplicated appendicitis suitable to be operated by laparoscopy.

Patients will be randomized to receive outpatient care (day-surgery) or conventional inpatient care with overnight hospitalization in the surgery department. The primary outcome is postoperative morbi-mortality at D30. Secondary outcomes include time from diagnosis to appendectomy, length of total hospital stay, re-hospitalization, interventional radiology, re-interventions until D30, conversion from outpatient to inpatient, and quality of life and patient satisfaction using validated questionnaires.

**Discussion** The SAMBA trial tests the hypothesis that outpatient surgery (i.e., without an overnight hospital stay) of uncomplicated acute appendicitis is a feasible and reliable procedure in establishments with a technical platform able to support this management strategy.

**Trial registration** ClinicalTrials.gov NCT05691348. Registered on 20 January 2023.

**Keywords** Appendectomy, Ambulatory surgery, Outpatient surgery, Postoperative morbi-mortality, Randomized controlled trial

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## Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

| **Title {1}** | **SAMe day amBulatory Appendectomy (SAMBA): a multicenter, prospective, randomized clinical trial** |
|---|---|
| Trial registration {2a and 2b}. | Clinicaltrials.gov Identifier: NCT05691348. This registration entry contains all items of the WHO Trial Registration Data Set |
| Protocol version {3} | This article is based on protocol version 3.0 of August 2, 2023 approved by the ethics committee (CPP Ouest II, France) on September 26, 2023 |
| Funding {4} | French Ministry of Health, Hospital clinical research program (PHRC) 2021 to Nice University Hospital |
| Author details {5a} | Co-Coordinating Investigators: Pr Catherine Arvieux and Dr Damien Massalou<br>Participating Investigators: Surgeons—Catherine ARVIEUX, Damien MASSALOU, Sandrine BARBOIS; Project manager—Fatah TIDADINI, Céline HIVELIN; CH Methodologist—Jean-Louis QUESADA, Eric FONTAS; Statistician: Coralie CRUZEL; Data-manager: Sabine ANTHONY; Medico-economist: Julie BULSEI; Medical writer – Fatah TIDADINI; Alison FOOTE |
| Name and contact information for the trial sponsor {5b} | Nice University Hospital, Clinical research and Innovation administration (DRCI). 4 Avenue Reine Victoria CS 91179, 06003 Nice Cedex 1, France |
| Role of sponsor {5c} | The study sponsor and the funder have approved the study design; but play no role in data collection, management, analysis, and interpretation of results; in writing of the report; or the decision to submit the report for publication. |

## Introduction

### Background and rationale {6a}

Acute appendicitis (AA) is one of the most frequent digestive pathologies requiring emergency intervention. It represents a major public health issue with, in France, more than 80,000 interventions annually (French National Hospitals Database, 2012). A retrospective study of adults and children admitted to French emergency or surgical units for acute appendicitis (APPEA for "APPendicite Aigue chez l'Enfant et l'Adult")' [1, 2] showed that patients were predominantly young and active with a peak incidence between 10 and 20 years. For adults laparoscopic surgery was the standard treatment, performed in 92.3% of patients, [2] and in line with recent guidelines [3]. Patients with uncomplicated appendicitis experienced an overall rate of complications of 5.4%. Severe postoperative complications (Clavien-Dindo [4] grade III–IV)) occurred in only 18/1240 (1.5%) of cases and the mortality rate was 0.2% |2]. We observed that adolescents aged 13–17 presented the same profile in terms of morbi-mortality as adults, in contrast to younger patients who more frequently had severe morbi-mortality [1]. This is confirmed by studies showing a decreasing risk of complicated appendicitis correlated with older age in children and adolescents [5]. For adults, the French data are comparable with the worldwide POSAW study (one of the largest studies on the subject). In this later study, a total of 287 patients (287/3117, 9.2%) developed complications, with a rate of major complications (Clavien-Dindo III–V) of 4.6% and 0.28% mortality [6].

In the APPEA, study [2] the severity of appendicitis was classified according to precise histological criteria, resulting in 75.8% of adult patients being classified as presenting with uncomplicated appendicitis. Many studies classify patients differently, according to preoperative clinical, laboratory, and radiological criteria [3, 7]; nevertheless, they similarly show that uncomplicated appendicitis accounts for three-quarters of patients.

A systematic review of the literature [8] suggested the feasibility of appendectomy with day hospitalization (< 12 h), and several non-randomized studies have confirmed that an outpatient intervention for selected patients does not increase overall morbidity, the readmission rate nor the repeat surgery rate. The same authors concluded that outpatient appendectomy appears feasible and safe, but that there is a lack of high-quality data and a randomized study is needed [8]. We hypothesize that outpatient management of uncomplicated acute appendicitis is a feasible and reliable procedure in establishments with a technical platform able to support this management strategy.

In France, the management of appendicitis in an outpatient setting remains underdeveloped and has been little evaluated. Outpatient management of acute appendicitis is done in a few centers in France, with organizational modalities varying widely, raising ethical and medico-legal issues. It seems not to cause any increase in morbidity compared to usual care, with the advantages of day hospitalization and high patient satisfaction. However, no randomized study has been published internationally. In terms of safety, we hypothesize that morbidity

due to appendectomy for uncomplicated acute appendicitis would be lower than that of other digestive surgical procedures commonly performed on an outpatient basis, such as laparoscopic colectomy.

If our hypothesis is confirmed, the possibility of outpatient surgery for a large proportion of appendectomies will allow organizational improvements, freeing hospital beds for the treatment of other urgent pathologies. Furthermore, the potential benefit of outpatient care for this common digestive emergency is considerable, both for the patients themselves and for the public health system.

From a medico-economic perspective, currently in France, there is no diagnosis-related group (DRG) for outpatient appendectomy. Effectiveness and cost data of outpatient appendectomy are needed by the French health care system in order for them to compare it to conventional inpatient appendectomy. If cost efficiency is confirmed, a national tariff for ambulatory appendectomy could then be fixed on the basis of data from the health-economic study. The goal is to encourage French hospitals to perform outpatient appendectomy in routine practice. Indeed, the lower costs of outpatient care, compared to conventional hospitalization, are an asset that allows the health care system to better control health care expenditure [9, 10].

#### Objectives {7}

##### *Primary objective*

The aim of this trial is to demonstrate that outpatient surgery (day hospitalization) compared with conventional surgery (involving at least one overnight hospital stay) in selected patients with acute uncomplicated appendicitis operated by laparoscopy, is non-inferior in terms of overall morbi-mortality assessed up to the 30th postoperative day.

##### *Secondary objectives*

To compare between the groups, at post-operative day 30:

a) The delay from diagnosis to appendectomy
b) The real cumulated length of hospitalization
c) The rehospitalization rate
d) The mild morbidity (Clavien-Dindo I–II) and the severe morbidity (Clavien-Dindo III, IV, V)
e) The rate of interventional radiology re-intervention (radio-guided drainage)
f) The rate of laparoscopic re-intervention
g) The rate of re-intervention by laparotomy

To compare between the groups:

h) Patient satisfaction at D7 and D30
i) Patient quality of life at D0, D7 and D30
j) Patient pain assessment at D0, at hospital discharge, D7 and D30
k) Pathological features
l) To evaluate the rate of conversion from outpatient to conventional care

##### *Health-economic objectives*

m) To estimate the cost of outpatient appendectomy management.
n) To study the economic impact of outpatient appendectomy management compared to conventional hospitalization.
o) To study the generalization of outpatient appendectomy management in all French hospitals.

#### Trial design {8}

This is a prospective open-label, multicenter, two parallel-group randomized controlled clinical non-inferiority trial. Patients who fulfill the inclusion criteria and do not present any of the exclusion criteria are randomized in a 1:1 manner to outpatient care (AMB) or to conventional (inpatient) care (CONV).

## Methods: participants, interventions, and outcomes

#### Study setting {9}

The trial is being performed in 33 hospitals (see Additional file 1), mainly University hospitals, located throughout France. All participating centers have an adequate technical platform and experienced surgeons for both outpatient (ambulatory) and inpatient digestive surgery.

#### Eligibility criteria {10}

*Inclusion criteria* are patients between 15 and 74 years old with uncomplicated acute appendicitis (fever less than 38.1 °C, no diffuse tenderness, white blood cell counts less than 15,000/mL, C-reactive protein less than 50 mg/L) confirmed by imaging (ultrasound and/or CT and/or MRI with no radiological signs of perforation and appendix diameter of 15 mm or smaller), BMI $\leq$ 30 kg/m$^2$, pain calmed by level 2 analgesics at maximum, and time between diagnosis and surgery less than or equal to 24 h. Patients must meet the hospital's outpatient surgery criteria, which in general are availability of a relative to accompany and monitor the patient's condition during the 12 h after discharge from the hospital; residence located less than 20 min by car from a health center (hospital, clinic or doctor's office); and access to a mobile or

fixed telephone mobile in case of problems. The written informed consent form must be signed by the patient, and if the patient is a minor (< 18 years), by both parents or their legal representative(s). Patients should be affiliated to or beneficiaries of the French health insurance scheme or equivalent.

*Non-inclusion criteria* are an ASA score > 2, severe or uncontrolled comorbidities, severe pulmonary disease (including obstructive sleep apnea), ongoing anticoagulation or antiplatelet drug therapy, or contraindication to ambulatory or outpatient surgery such as intubation difficulties, active cancer, a malignant hemopathy or suspicion of a tumor of the appendix, drug addiction, coagulopathy, or immunosuppressive treatment. Also, patients with non-acute or interval appendicitis (i.e., after antibiotic treatment of complicated appendicitis of the plastron or drainage of an appendicular abscess), those with a history of pelvic surgery, pregnant or breast-feeding women and adults under guardianship or legally deprived of freedom will not be included.

*The exit criterium* is the withdrawal of consent.

#### Who will take informed consent? {26a}

In each trial center, informed consent is obtained by the center's trial investigator in charge of the patient, at the inclusion visit (D0).

#### Additional consent provisions for collection and use of participant data and biological specimens {26b}

In the patient information sheet participants are informed that their de-identified data might be used for research purposes. They have the right to refuse that their data is used. No biological samples are specifically collected and stored for the study or future researches.

## Interventions

#### Explanation for the choice of comparators {6b}

Outpatient appendectomy (day hospitalization) is compared with conventional care (involving at least one overnight hospital stay) which is the current usual practice in France and hence the natural choice for the control intervention.

#### Intervention description {11a}

***Preoperative course and surgery (V1)***

*All included patients* Preoperative antibiotherapy is mandatory for all patients if surgery is not performed within 8 h of diagnosis. In this case, antibiotics will be given to patients 8 h after diagnosis, then every 8 h until surgery, without exceeding 24 h.

The preoperative Prophylactic Antibiotherapy Protocol (ATBProt) is amoxicillin (penicillin) + beta lactams-inhibitors (Augmentin):

- For adults: 1000 mg/125 mg, three times a day;
- For patients weighing less than or equal to 40 kg: 80 mg/10 mg per 10 kg and per day, in 3 doses.

In case of allergy to penicillin, the association of levofloxacin and metronidazole is recommended [9]:

- For adults: levofloxacin 500 mg twice a day and metronidazole 500 mg three times a day;
- For patients weighing less than or equal to 40 kg: levofloxacin 10 mg/kg in two doses and metronidazole 30 mg/kg in three doses.

*Control group* Patients randomized to conventional inpatient appendectomy (CONV):

- Hospitalization in the digestive surgery department as soon as the diagnosis is confirmed (Ultrasound, CT scan, or MRI)
- Intervention as soon as possible (within 24 h of diagnosis) by laparoscopy under general anesthesia as soon as an operating room and surgeon becomes available, in line with the "Jerusalem" guidelines [3].
- One night of hospitalization in a conventional postoperative ward.

*Intervention group* Patients randomized to outpatient (ambulatory) appendectomy (AMB):

- Immediate day-hospitalization in the outpatient surgery unit and intervention the same day if all the deadlines for carrying out the intervention can be met (availability of surgeon, anesthetist and operating room, a preoperative fast of 2 h for liquids and 6 h for solid food, availability of results of laboratory analyses) and sufficient duration for postoperative monitoring (established jointly between the anesthesist and the surgeon) to allow discharge from the hospital the same day (i.e., admission before 1 p.m.).
- If study inclusion is late (admission after 1 p.m.), the patient returns home with antibiotic therapy and analgesics. The patient is scheduled back the next day for day hospitalization and surgery on an outpatient basis.
- Appendectomy is performed by laparoscopy under general anesthesia. After surgery, the patient is transferred to the surgery recovery ward.

#### *Immediate post-operative course (V2 and V3)*

*Both groups* Administration of peroperative and post-operative antibiotics is left to the investigator's discretion, according to the current practice and the patient's medical condition.

All included patients will have a physical examination and pain assessment after surgery.

In both groups the discharge of patients is made by the surgeon and authorized if:

- Pain is controlled by level 1 and/or 2 oral analgesics. The treatments prescribed as well as any nursing care are identical to those prescribed in current practice. The prescriptions will be given to the patient.
- An oral diet is well tolerated.
- Absence of occurrence of other complications.

All patients are encouraged to download the Link4Life application on their smartphone; alternatively, they can complete paper versions of the questionnaires and pain VAS scores. The Link4Life application (see Additional file 2) was designed and developed by doctors to allow patients to be monitored at home. It enables assessment scores and follow-up questionnaires to be sent at previously defined times. If the patient does not complete the questionnaires, a notification is sent to the investigator and to the local study CRA. In the event of non-response from the patient on the application, or if the patient does not have a smartphone, the CRA of the associated investigation center is responsible for collecting the data by phone.

*Intervention group (AMB) only* Before discharge (D0):

- Chung score (medical conditions for discharge of patient following outpatient care) > 8/10 [11].
- Check the hospital's outpatient surgery discharge criteria are met.

Phone call on day 1 (D1) of postoperative course by a staff nurse of the outpatient team (V3). This will include:

- A pain assessment
- Questions to search for the occurrence of complications
- Questions to determine and collect details of any adverse (AE) and/or serious (SAE) or unexpected SAE (USAE).
- A reminder to the patient to complete the EQ-5D-5L quality of life questionnaire and satisfaction assessment (via the Link4Life application or paper versions) on D7.

*Control group* No phone call on D1.

#### *Short-term follow-up (V4)*

*Both groups* Follow-up on D7 + / − 2 days (remotely, using Link4Life application or paper versions of questionnaires).

- A pain assessment (VAS)
- Questions to search for the occurrence of complications.
- Questions to determine and collect details of any adverse (AE) and serious (SAE and USAE) events
- EQ-5D-5L, quality of life questionnaire
- Patient satisfaction assessment on a numerical scale from 0 to 10. For patients using the Link4Life app: if they fail to answer the questions, a reminder is sent automatically.

If the patient cannot use Link4Life, they are contacted by a staff nurse or the local CRA.

#### *Mid-term follow-up (V5)*

*Both groups* Follow-up on D30 + / − 12 days:

All patients are seen in consultation 30 days + / − 12 days (D30) post-operatively. All hospital readmissions or unscheduled consultations in the emergency department (or elsewhere) are noted. Any complications are recorded with morbi-mortality classified according to the Clavien-Dindo classification [4]. The pathologic results from the surgical specimen are described.

Patients are asked for pain assessment and to complete the EQ-5D-5L quality of life questionnaire and satisfaction questionnaire.

The participation of the patient in the study ends after the D30 visit, and their usual follow-up is resumed based on the guidelines concerning their condition.

### Criteria for discontinuing or modifying allocated interventions {11b}

For patients randomized to outpatient appendectomy (AMB) conversion to conventional care, i.e., inpatient hospitalization, is possible if the patient does not meet the conditions for discharge the same day.

### Strategies to improve adherence to interventions {11c}

NA. The hospitalization lasts less than 24 h or 2–3 days, depending on the group.

**Relevant concomitant care permitted or prohibited during the trial {11d}**

In the best interest of the patient, all relevant concomitant care and interventions are permitted including conversion from outpatient to inpatient care.

The Prophylactic Antibiotherapy Protocol (ATBProt) is amoxicillin (penicillins) + beta-lactams inhibitors and in case of allergy to penicillin the association of levofloxacin and metronidazole as recommended in the "Jerusalem" guidelines [3] beginning in both group at H8 after the diagnosis.

**Provisions for post-trial care {30}**

After the end-of-trial visit on D30 for both groups, patients are recommended to consult their family practitioner in the event of pain or another health problem as it is done in routine practice.

**Outcomes {12}**

***Primary outcome***

*Morbi-mortality up to postoperative D30* Morbi-mortality is classified according to the Clavien-Dindo classification 0-V, which has been objectively validated for all surgical specialties [4]. This classification ranks complications from 0 (no complication) to V (death).

***Secondary outcomes***

a) Time from diagnosis to appendectomy: defined as the time between the CT scan (or ultrasound or MRI) and the skin incision (in minutes)
b) Cumulative length of the entire hospital stay(s) in hours until D30
c) All re-hospitalization(s) for any cause after initial discharge until D30
d) Postoperative mild morbidity according to Clavien-Dindo classification (grade I, II) and severe morbidity according to Clavien-Dindo classification (grade III, IV, V) up to D30.
e) All interventional radiology re-interventions (e.g., radio-guided drainage) until D30
f) All laparoscopic re-interventions performed until D30
g) All the laparotomic re-interventions performed until D30
h) Patient satisfaction assessed using a numerical scale from 0 to 10, via the Link4Life smartphone app, or phone, at D7 and D30.
i) Quality of life using a standardized questionnaire, the EuroQol five-dimension questionnaire (EQ-5D-5L) questionnaire, at D0 (during the inclusion visit), D7 and D30, using the Link4Life smartphone app.
j) Pain assessment using a visual analog scale (VAS) graduated from 0 to 10, with higher scores for higher pain
k) Any conversion, defined as a patient randomized to the outpatient appendectomy group who is finally treated following the conventional care procedure.
l) Peroperative features defined as clinical parameters as the type of appendicitis, the type of complicated appendicitis if any, the presence of a stercolith or of a peritonitis
m) Pathological features (from the pathological resume) defined as pathological parameters as the type of appendicitis, the type of complicated appendicitis if any, the presence of a stercolith or appendicular tumor

***Health-economics outcomes***

n) The cost to the hospital of outpatient appendectomy management
o) The economic impact will be studied with a cost-utility analysis ( incremental cost-effectiveness ratio (ICER) in cost per QALY gained) and a cost-effectiveness analysis (ICER in cost per patient without rehospitalization)
p) The generalization of outpatient appendectomy management in all French hospitals will be studied with a budget impact model

**Participant timeline {13}**

The patient flowchart is shown in Fig. 1 and schedule of enrolment, interventions, and assessments in Fig. 2. The duration of participation for each patient is 1 month.

**Sample size {14}**

Based on the available publications [6, 12, 13] and our experience [2] the overall rate of complications (Clavien-Dindo classification I–V) [4] at D30 after appendectomy is estimated to be between 7 and 9%. With a selected population with uncomplicated appendicitis, we showed a rate of complications of 5.4% [2] with a range between 3.5 and 8% in two other studies [7, 14]. Thus, we will use as reference an expected rate of complications at D30 of 5.5%, and set the threshold for non-inferiority at + 3.5%. For a power of 80% and an α error rate for unilateral significance set at 0.025, the calculated sample size is 667 per group, i.e., 1334 patients in total (Nquery v 9.1, Non-inferiority Test for two proportions). To account for a 5% rate of loss to follow-up, the total sample size is 1400 patients. According to the potential for recruitment of the participating centers,

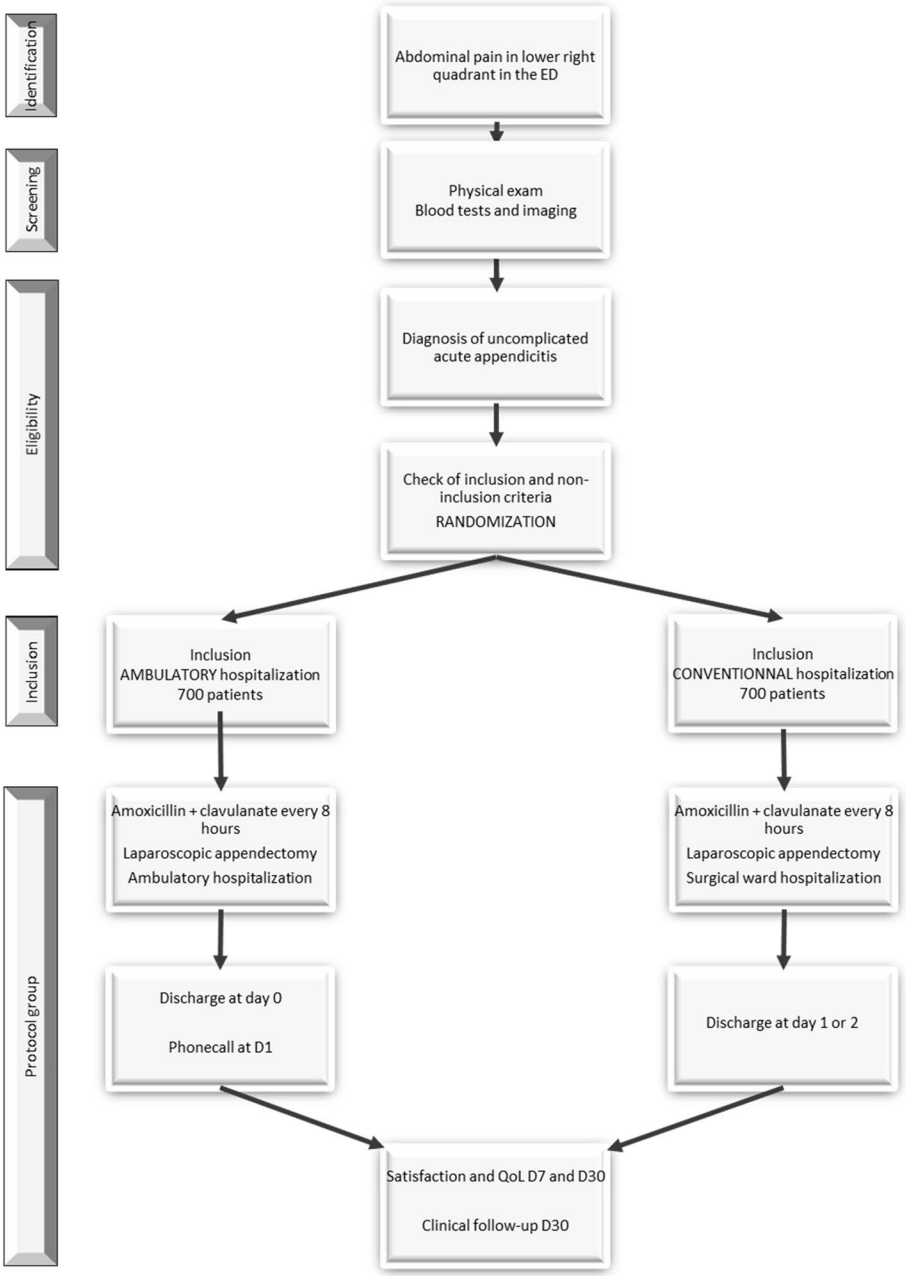


**Fig. 1** Study flowchart

which ranges between 5 and 20 patients per month (depending on the size of the hospital), it seems reasonable to plan a recruitment period of 30 months. With this conservative timeframe, the number of patients to include per center is about 1.5 per month which seems to be a highly feasible target.

#### Recruitment {15}

Patients are fast tracked and screened for eligibility from among all patients who are referred to or arrive directly at the participating hospitals presenting acute appendicitis.

## Assignment of interventions: allocation

#### Sequence generation {16a}

Balanced (1:1) randomization (randomly mixed block sizes) will be carried out by the Delegation of Clinical Research and Innovation (DRCI) at Nice University Hospital using Nquery© Advisor v 7.0 software. The randomization will be stratified by center.

| **Visit** | V0 | V1 | V2 | | | V3 | V4 | V5 |
|---|---|---|---|---|---|---|---|---|
| **Study stage** | Inclusion visit | Intervention (surgery) | In-hospital post-operative monitoring and discharge | | | Postoperative follow-up | | |
| Delay from D0 | D-1 | D0 | D0 | Between D1 and D5 | | D1 | D7 +/- 2 days [1] | D30 +/- 12 days |
| Interval | | | AMB arm | CONV arm | | AMB arm | AMB and CONV arms | |
| Location | Surgery Preoperative consultation | Hospitalisation (care) | | | | Home (telephone follow-up) | | Digestive surgery consultation |
| EQUIPE CLINICAL DATA | | | | | | | | |
| Check inclusion / Non-inclusion criteria | X | | | | | | | |
| Patient information and signature of consent form | X | | | | | | | |
| Consultation with surgeon | X | | | | | | | |
| EQ-5D-5L questionnaire | X | | | | | | X | X |
| Clinical Examination | X | | X | X | | | | X |
| Pain evaluation | X | | X | X | | X | X | X |
| Samples sent to biological laboratory (usual care) | X | X | | | | | | |
| Surgery | | X | | | | | | |
| CHUNG score | | | X | X | | | | |
| **RANDOMIZATION** | **X** | | | | | | | |
| Phone call to patient by staff nurse or local CRA | | | | | | X | X [1] | |
| Collection of post-operative complications | | X | X | X | | X | X | X |
| Collection and reporting of AE and SAE | X | X | X | X | | X | X | X |
| Satisfaction questionnaire | | | | | | | X | X |
| Clavien-Dindo classification | | | | | | | | X |
| Collection of healthcare consumption data (medico-economic study) [2] | | | | | | | X | X |

**Fig. 2** Schedule of enrolment, interventions, and assessments

### Concealment mechanism {16b}

Randomization will be integrated in the electronic case report file (e-CRF) developed specifically for the study using RedCap® software. Access to the online randomization module is restricted to trial investigators and requires individual passwords.

### Implementation {16c}

After obtaining signed informed consent from all parties, the trial investigator logs in to the study e-CRF using their personal access codes (randomization is available 24/24) and completes the necessary information about the patient. The system then randomly allocates the patient to one or other of the study arms.

## Assignment of interventions: blinding

### Who will be blinded {17a}

NA. Neither the patients nor their clinicians are blinded to treatment assignment due to the nature of the interventions. Data analysts will be blinded to the randomization arms.

### Procedure for unblinding if needed {17b}

NA. Neither the patients nor their clinicians are blinded to treatment assignment due to the nature of the design.

## Data collection and management

### Plans for assessment and collection of outcomes {18a}

Patient characteristics, baseline, and follow-up data will be recorded in standardized electronic case report forms (e-CRFs) developed using RedCap® software. The demographic data of the patient, their medical history, and ongoing treatments will be recorded at the inclusion visit. Data for the outcome variables will be recorded in e-CRFs for the surgical procedure, hospital stay, D1, D7, and D30 follow-up. Quality of life will be assessed using the EQ-5D-5L questionnaire completed by the patient through the Smartphone application Link4Life at inclusion (D0), and postoperative D7 and D30 where satisfaction is also assessed. Patients not willing to use the application Link4Life will be proposed to fill in a paper version of the EQ-5D-5L questionnaire.

Data collected through the Link4Life application will be extracted and imported into the e-CRF in pre-existing fields in order to centralize all the collected study data.

### Plans to promote participant retention and complete follow-up {18b}

The main outcome is collected at the routine post-operative consultation, which occurs at postoperative D30 irrespective of participation in the trial.

### Data management {19}

The e-CRF is filled in by the trial investigators or the study project manager at inclusion before surgery, during the entire hospitalization, and postoperative D1, D7, and D30. The sponsor's clinical research assistant monitors the trial data of all patients based on risk management.

Once the final data have been entered, their validity and coherence will be checked by the Data Manager of the DRCI (Nice) who will control, among others, missing data and data incoherencies. Any requests for data verification and corrections will be issued by sending queries.

Throughout the study, any modifications to the database will be recorded, thereby enabling a full audit trail. Access to the database will be controlled via person-specific login.

At the end of the quality control process, the database will be locked and signed off by the principal investigator, the data manager, and the head of the biometrics unit at the DRCI. No modification of the data will be possible after this time. The locked database, together with the data management report, will then be transferred to the statistician for analysis.

The entire data management process is described in the Data Management Plan of the trial.

### Confidentiality {27}

All patient data are pseudo-anonymized. The study was registered in the internal register of the Nice University Hospital of studies respecting the reference methodology MR001 of the French National Commission for Informatics and Freedoms (CNIL).

### Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

NA There is no storage of biological specimens for genetic or molecular analysis either in the current trial or for future use.

## Statistical methods

### Statistical methods for primary and secondary outcomes {20a}

The study patient data will be analyzed according to the per-protocol principle. Patients with a major protocol deviation will be removed from the analysis.

An intention-to-treat (ITT) analysis will also be performed, each patient will be analyzed as part of the group to which he or she was assigned at randomization. The results of this analysis will not be substituted for those of per protocol analysis.

Due to the short duration of the study for patients, we expect very little missing data, and so there will be no replacement of missing data in the clinical study.

Before each analysis is performed the conditions for the application of the tests to be used will be verified. The various test results will be considered significant at a threshold of 5% (unless otherwise specified). The statistical analysis will be performed using SAS Enterprise Guide 4.1 software (Copyright (c) 1999–2006 by SAS Institute Inc., Cary, NC, USA).

Analysis of the primary objective will be realized using a logistic regression model. The dependent variable will be the presence or not of at least one complication over the follow-up and the group as the variable of interest. The model will be adjusted on the center (stratification parameter). A mean number of events per patient will be presented in each group as well as the distribution of the events in each group according to the Clavien-Dindo classification.

A detailed preliminary statistical analysis plan (SAP) is presented in Additional file 3).

### Interim analyses {21b}

N/A No interim analyses are planned.

**Methods for additional analyses (e.g., subgroup analyses) {20b}**
N/A No additional analyses are planned.

**Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}**
There will be no missing data replacement in the clinical study. In the health economics study, missing data will be imputed either by the average in the case of quantitative variables or by the weighted frequency in the case of qualitative variables. Multiple imputation will be performed in the case of missing data for the effectiveness criteria.

**Plans to give access to the full protocol, participant-level data and statistical code {31c}**
The full protocol, the de-identified participant-level dataset, and the statistical code will be made available to researchers on reasonable request to the sponsor (Nice University Hospital Clinical Research Administration).

## Oversight and monitoring

**Composition of the coordinating center and trial steering committee {5d}**
The digestive surgery unit of Nice University Hospital is the coordinating center and works in close collaboration with the digestive surgery department of Grenoble-Alpes University Hospital. There is no external steering committee and no Stakeholder and Public Involvement Group (SPIG). The outcome/endpoint adjudication committee has not been nominated yet.

**Composition of the data monitoring committee, its role and reporting structure {21a}**
We do not anticipate any impediments to patient inclusion or significant adverse or serious adverse events. As a result, no data safety advisory board is required during the study.

**Adverse event reporting and harms {22}**
All adverse events during the study period are reported on the e-CRF. The severity is classified by the Clavien-Dindo classification and rehospitalizations and reinterventions are registered, as well as the evolution and imputability.

Severe adverse events are declared to the pharmacovigilance unit and authorities within 24 h of occurrence, in accordance with French regulations.

**Frequency and plans for auditing trial conduct {23}**

1. Project management group:

   A first monitoring visit will be scheduled after 2 patients have been included by the center (+ 2 months).
   - If by 8 months following the inclusion of the first patient, there has been no other inclusion the first monitoring will be done.
   - Then monitoring after every 10 patients included (+ 2 months) until the end of the study.
   - If within 18 months following the 2nd inclusion, 10 additional patients have not been included, monitoring will be triggered.

2. Data safety monitoring board (DSMB)
   We do not anticipate any impediments to patient inclusion or significant adverse or serious adverse events. As a result, no data safety advisory board is required during the study.

**Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}**
The investigators, clinical research assistants, digestive surgery unit nurses, the ethics committee, and the sponsor are immediately informed by email of any changes in the protocol.

**Dissemination plans {31a}**
The trial results will be presented at appropriate French and international conferences and submitted for publication in a medical journal. The authorship guidelines of the ICMJE will be followed. Dr Foote, a native English clinical researcher and medical writer will help write the manuscript. The present article presents the trial protocol. Interested patients can be informed of the results through the Nice or Grenoble-Alpes University Hospital websites.

## Discussion

In the only review of the literature about same-day ambulatory appendectomy, it is stated that there is a lack of high-quality comparative studies to support conclusive recommendations for outpatient appendectomy [8]. As far as we know, no prospective randomized study has been published internationally on the specific subject of outpatient management of appendicitis. The first retrospective study published in 2015, analyzed more than 400 appendectomies. Predictive factors of same-day discharge were body mass index less than 28 kg/$m^2$, WBC less than 15,000/mL, CRP less than 30 mg/L, no radiological signs of perforation, and appendix diameter of 10 mm or smaller [7]. In another study, an appendicolith was found to be an independent risk factor for unexpected re-hospitalization [15]. Also, patients needed to meet classical outpatient criteria such as a low ASA score (ASA 1 or 2) and the absence of a severe comorbidity.

In France, the benefits of ambulatory care for many straightforward surgical procedures in terms of patient satisfaction, as well as at the medico-economic level, are well established [9, 10]. Regarding appendectomy, the "Jerusalem" guidelines recommend against delaying appendectomy for acute appendicitis beyond 24 h from admission [3]. However, in the French APPEA study [2] 17.2% of the patients underwent surgery more than one day after admission. We showed that a delay before surgery of 2 days or more was almost twice as frequent in regional hospitals (9.3%) than in university hospitals (4.5%). Surgery for appendicitis appears to have less delay in the USA: a study with 32 782 patients showed that 75.2% of the patients underwent operations within 6 h of hospital admission, 15.1% at more than 6 through 12 h, and 9.8% at more than 12 h after admission [16]. Moreover, in France, the mean length of stay for appendicitis was 3.75 days for adults aged between 18 and 74 years [2] which is untenable from medico-economic and patient satisfaction points of view. The length of hospitalization observed in France seems disproportionate regarding a pathology that concerns young and otherwise healthy patients, and which is in 75% of the cases has a rate of complication of under 6%. The main explanation is the low availability of surgical ward beds. Surgery patients can wait in the emergency department for prolonged periods of time before obtaining access to surgery [17]. Moreover, logically, in the event of limited availability of operating rooms patients with the less severe pathologies, such as uncomplicated appendicitis, will remain at the end of the waiting list, after elderly patients, those with severe comorbidities, and/or a more life-threatening pathology.

In our opinion, the two obstacles to the management of appendicitis on an outpatient basis are (i) the absence of a consensus management protocol including validated clinical, biological laboratory, and radiological criteria, and (ii) the reluctance of surgeons. As we consider it essential to convince medical and surgical teams of the individual benefit for patients presenting uncomplicated appendicitis, we have chosen to demonstrate that outpatient management of uncomplicated appendicitis shows comparable overall morbidity (Clavien-Dindo grades III to IV) to the conventional inpatient approach (primary outcome). The alternative choice would have been to take severe morbidity as the main criterion, but this was not retained because the expected rate of this outcome in this category of patients (1–3%) is too low to have any statistical meaning.

We chose to assess the primary endpoint at postoperative D30 because a medical consultation at this time is usual practice in France, and it allows investigators to collect both short-term and mid-term postoperative complications. This consultation also makes it possible to ensure proper wound healing and the possible resumption of socio-professional and sporting activities.

Concerning the age range of patients: in the APPEA study [1], the median age of the patients was 20 years with 45% of patients under 18 (age of majority according to French law). Usually, in French university hospitals, the lower age limit of patients admitted to adult departments is 15 years. Most of the participating centers are adult surgery departments, hence, we choose to include patients over 15 years so as not to lose a significant part of the population with appendicitis and also for the study population to be representative of the population followed in the participating centers. Patients aged 75 and more with a clinical presentation of appendicitis have a significantly higher incidence of underlying right colic cancer [18].

Surgery remains the gold standard for the treatment of acute appendicitis. Nevertheless, the strategy of antibiotic therapy alone is often debated, but the significantly higher rate of complications explains why this approach has never been adopted in a sustainable way. However, in line with recommendations when surgery is not immediately available a preoperative course of antibiotics is included in this protocol.

## Conclusion

The SAMBA trial includes selected patients with acute uncomplicated appendicitis operated by laparoscopy. It is an international prospective randomized controlled open trial, designed to assess the non-inferiority of overall morbi-mortality at postoperative day 30 of outpatient surgery compared with conventional surgery involving at least one overnight hospital.

If our hypothesis is confirmed, the extension of outpatient surgery for selected patients experiencing common digestive emergencies, such as acute cholecystitis, may be expected. Furthermore, a reduction in the average length of hospital stay for appendectomies should make significant savings for both public and private health insurance schemes while increasing financial savings for hospitals.

## Trial status

The first patient was randomized on July 17$^{th}$, 2023 and recruitment will be completed on December 31, 2025. At the time of submitting this protocol (version n°4.0 on 05/02/2024) for publication (April 24, 2024), 33 centers were actively recruiting patients for the trial and 71 out of 1400 (5.07%) have been randomized.

**Abbreviations**

| | |
|---|---|
| AA | Acute appendicitis |
| AFC | French Association of Surgery Group-Association Française de Chirurgie |
| APPEA | Acute Appendicitis in children and adults-APPendicite de l'Enfant et de l'Adulte |
| BMI | Body mass index |
| CNIL | National Commission for Information Technology and Freedoms |
| CRA | Clinical research assistant |
| CRF | Case report form |
| DRCI | Delegation of Clinical Research and Innovation |
| HAS | French National Authority for Health |
| ICER | Incremental cost-effectiveness ratio |
| IRB | Institutional Review Board |
| ITT | Intention-to-treat |
| MRI | Magnetic resonance omaging |
| QALY | Quality-adjusted life years |
| QoL | Quality of life |
| US | Ultrasound |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08336-x.

Additional file 1: List of centers and investigators

Additional file 2: Supplementary Material

Additional file 3: Statistical Analysis Plan

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Not Applicable.

**Authors' contributions {31b}**
CA and DM are the trial coordinators and senior investigators; CA, FT, and SB conceived the study and led the proposal and protocol development. DM, MC, VG, and JCO contributed to the study design and to development of the proposal. JLQ and EF are the lead trial methodologists. FT and CH are project managers. FT and AF are the medical writers. All authors have read and approved the final manuscript.

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**Availability of data and materials {29}**
The study data will be available upon reasonable request to the corresponding author.

## Declarations

**Ethics approval and consent to participate {24}**
The trial protocol was approved by the French ethics committee ("Comité pour la protection de personnes" CPP) Ouest II on November 22, 2022, and the most recent amended version on August 2, 2023 (IRB n° 2022-A01848-35). Signature of the written informed consent form by the patient is required prior to inclusion in the trial. If the patient is a minor, a signature of the written informed consent form by both parents or their legal representative(s) is required.

**Consent for publication {32}**
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

**Competing interests {28}**
The authors declare that they have no competing interests.

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## Publisher's Note