study, based on readiness of infrastructure, staff engagement, patient population characteristics, and number of appendicitis cases.

Prior to study initiation and enrollment, all clinicians and staff who encounter patients with possible appendicitis will complete study-specific training including demonstrating successful use of the antibiotics strategy in five patients and site experience recorded in a non-protected health information (PHI) based registry (www.certain.org/appysurvey) or log reviewed with the study leadership team. All staff engaging patients with appendicitis at all study sites will undergo online and in-person educational and orientation sessions for the topic and the study protocol.

Table 1. Potential Study Sites, Characteristics, and Projected Yearly Volume of Appendicitis.

Medical Center	Total n/yr	N (%)							
		Female	> 65 Years	Medicaid	Hispanic	Black	Asian	AI/AN*	Pacific Islander
Harborview	47	13 (27.7)	2 (4.3)	12 (25.5)	12 (25.5)	7 (14.9)	7 (14.9)	2 (4.3)	4 (8.5)
Madigan Army	107	33 (53.6)	16 (15.0)	0 (0.0)	4 (3.7)	4 (3.7)	2 (1.9)	0 (0.0)	1 (0.9)
Northwest	77	36 (46.8)	14 (18.2)	8 (10.4)	2 (2.6)	6 (7.8)	6 (7.8)	0 (0.0)	0 (0.0)
Providence	294	147 (50.0)	54 (18.4)	47 (16.0)	26 (8.8)	6 (2.0)	16 (5.4)	5 (1.7)	3 (1.0)
Sacred Heart	180	91 (50.6)	35 (19.4)	18 (10.0)	2 (1.1)	4 (2.2)	2 (1.1)	4 (2.2)	1 (0.6)
Skagit Valley	93	57 (61.3)	21 (22.6)	17 (18.3)	20 (21.5)	3 (3.2)	1 (1.1)	2 (2.2)	0 (0.0)
Swedish	386	179 (46.4)	67 (17.4)	20 (5.2)	35 (9.1)	11 (2.9)	39 (10.1)	0 (0.0)	3 (0.8)
University of Washington	85	38 (44.7)	14 (16.5)	12 (14.5)	8 (9.4)	1 (1.2)	10 (11.8)	2 (2.4)	0 (0.0)
Virginia Mason	87	41 (47.1)	26 (29.9)	2 (2.3)	4 (4.6)	3 (3.5)	8 (9.2)	1 (1.2)	2 (2.3)
Olive View-UCLA	221	85 (38.5)	2 (0.9)	173 (78.3)	183 (82.8)	2 (0.9)	6 (2.7)	0 (0.0)	4 (1.8)
Harbor-UCLA	263	112 (42.6)	4 (1.5)	116 (44.1)	229 (87.1)	19 (7.2)	8 (3.0)	0 (0.0)	0 (0.0)
Los Angeles County+USC	360	148 (41.1)	23 (6.4)	133 (36.9)	236 (65.6)	54 (15.0)	21 (5.8)	1 (0.3)	1 (0.3)
All Sites	2200	980 (44.5)	278 (12.6)	558 (25.4)	761 (34.6)	120 (5.5)	126 (5.7)	17 (0.8)	19 (0.9)

4.0 Participant Screening and Enrollment

4.1 Participant Screening

Patients presenting to the ED will be screened by study investigators and/or study coordinators seven days a week (6am-midnight) based on alerts from clinicians, staff, or screening of ED logs. Patients will be identified as potential candidates for the study based on inclusion and exclusion criteria collected as part of standard care, including confirmatory diagnostic imaging (CT, US, and/or MRI).

4.2 Inclusion Criteria

1. Adult ≥18 years;
2. Clinical diagnosis of acute uncomplicated appendicitis (AUA) established by clinical care team, supported by any of the following usual care radiological tests (CT,US, and/or MRI). AUA is defined by the usual signs, symptoms, and imaging finding of appendicitis **without**:
    a. Diffuse peritonitis on clinical exam (i.e., rigid abdomen / four quadrant peritonitis);

b. Radiologic findings of :
    i. Free air;
    ii. Walled off fluid collection concerning for an abscess;
    iii. Significant amounts of intra-abdominal fluid throughout abdomen (i.e., more than trace fluid); or
    iv. Extent of inflammation or adjacent organ involvement on radiologic imaging such that appendectomy is relatively contraindicated.

3. Ability to provide written or electronic informed consent in English or Spanish.

4.3 Exclusion Criteria

Participants must not have any of the following exclusion criteria:

1. Unable or unwilling to return or be contacted for clinical follow-up visits and/or research surveys;
2. Currently incarcerated in a detention facility or in police custody (patients wearing a monitoring device can be enrolled) at baseline/screening;
3. Evidence of severe sepsis or septic shock (e.g., new presumed sepsis-related organ dysfunction, elevated lactate, and/or fluid unresponsive hypotension);
4. Conditions with altered immune response or at risk for bacterial seeding;
5. Immunodeficiency (e.g., absolute neutrophil count <500/mm^3, chronic immunosuppressive drugs, active chemotherapy or plans for chemotherapy in the following 30 days, or known AIDS [CD4 count <200 or AIDS-defining illness within the last year] assessed by patient history);
6. Uncompensated liver failure;
7. Taking medication to treat active inflammatory bowel disease (e.g., Crohn's, ulcerative colitis);
8. Malignancy, not in remission (ongoing chemotherapy patients excluded);
9. Pregnant or expectation of becoming pregnant in the 30 days following baseline/screening;
10. Expected concurrent hemodialysis, peritoneal dialysis, or treatments using indwelling venous catheters;
11. Recent (within 90 days) placement of surgical implant (e.g., pacemaker, joint prosthesis, mechanical valve);
12. Indwelling Left Ventricular Assist Device (LVAD);
13. Patients with another infection (e.g., pneumonia, urinary tract infection) that requires treatment with another antibiotic at baseline/screening;

14. Concurrent illness that would otherwise mandate hospitalization outside of appendicitis and associated symptoms at baseline/screening;
15. Imaging findings of any of the following:
    a. Appendiceal soft-tissue mass;
    b. Imaging features of mucocele or tumor (e.g., appendix measuring ≥ 15mm in diameter and no other CT evidence of appendicitis);
    c. Concern for carcinomatosis on imaging; or
16. Severe allergy or reaction (e.g., immediate urticaria or anaphylaxis) to all of the proposed antibiotics (See Section 4.5);
17. Prior enrollment in the study or other investigational drug or vaccine while on study treatment;
18. Abdominal/pelvic surgery in the past month; or
19. More than seven hours have transpired since the patient received the first parenteral dose of antibiotics.

4.4 Consent Process

The research coordinator and a representative from the surgical team will confirm the patient's eligibility for the study based on inclusion and exclusion criteria. A research team member will approach all eligible patients and ask them to review an informed decision making video using a handheld device. The English or Spanish-language video explains both the treatment options and the research study using linguistically and culturally appropriate language. In the event that the tablet is malfunctioning, the research coordinator will provide an informational pamphlet that includes the same content as the video. The video and informational pamphlet both conclude with a request of the patient to read and sign an informed consent document for participation in the randomization cohort.

a. For patients consenting to randomization, they will be randomly assigned to either the antibiotics or appendectomy arm immediately following consent and assigned a study ID;
b. Patients refusing consent to randomization will be invited to participate in either the observational cohort or EMR review cohort. This will be done by separate consent with the participant selecting one of two participation options:
    - Option 1. Observational cohort (no randomization). Participants selecting the observational cohort will be asked to complete the same research assessment activities as the randomized cohort.
    - Option 2. EMR review cohort. Participants selecting this option will be followed by passive EMR review only. They will not be contacted again for study purposes and will not be asked to complete the Baseline Assessment or the Follow-Up Assessments described in Section 5.2.

In summary, there will be two consents for this study with the option to participate in the following groups: 1) randomization cohort, 2) observational cohort, and 3) EMR review cohort. Participants may only consent to one study group. The randomization consent will be presented to the patient following the informed decision-making video or material presentation. Patients declining randomization will then be presented with a different consent form to consider participation in either the observational cohort or EMR review only cohort.

4.4.1 Randomization Procedures

After informed consent, participants will be randomized to appendectomy or to antibiotics using computer generated assignments. Randomization will be based on a random number sequence, stratified by site and blocked to assure balance across treatment groups, presence of appendicolith, and sites. Randomization failures (defined as a patient who agreed to randomization but whose treatment was allocated in a non-random fashion) will be recorded as protocol deviations and these consenting participants will continue to be followed in the observational cohort. Their outcomes will be recorded and examined in a separate sub-analysis.

4.4.2 Those who Decline Randomization

All participants who decline randomization will be approached to provide consent to the observational cohort. As many as 500 will be asked to participate in an observational cohort study. Recruitment will be capped by treatment choice, site location, and time such that 14 participants from Washington sites and 7 participants from California sites may join the observational cohort per treatment arm per quarter. Once the cap has been reached, participants will be offered participation in the EMR review only cohort.

4.5 Antibiotics Therapy Arm

Patients in the antibiotics arm will receive a total of 10 days of antibiotics, with a minimum of 24 hours using an IV antibiotic formulation (administered in q8, q12, or q24 hour regimens with or without concurrent oral antibiotics) followed by oral antibiotics for the remainder of the 10 days. Patients will be offered a treatment regimen of antibiotics based on guidelines published jointly by the Surgical Infection Society and the Infectious Disease Society of America.[19] The first dose of antibiotics will be given in the ED at the time of diagnosis of appendicitis for both treatment arms. This flexibility in antibiotics choice is not expected to impact outcome but should improve the generalizability of the results, therefore, implementation of the findings. Any of the IV antibiotics options (*Single antibiotic*-Cefoxitin, Ertapenem, Moxifloxicin, Tigecycline, Ticarcillin-Clavulanic Acid or *Dual antibiotics*-Metronidazole plus one of the following-Cefazolin, Cefuroxime, Ceftriaxone, Cefotaxime, Ciprofloxacin, Levofloxacin) will be considered acceptable. At many sites, these will be administered to inpatients only. For clinicians and patients interested in outpatient receipt of antibiotics, the available options will include Ertapenem or Moxifloxacin (q24) alone or Ceftriaxone (IV) plus oral Metronidazole or Clindamycin, as tolerated. Although these antibiotics are considered acceptable and equally efficacious for intra-abdominal infections by the aforementioned professional societies, outcomes based on antibiotics used and antibiotics regimen will be monitored at regular intervals by the DCC and reported to the Data and Safety Monitoring Board (DSMB) for

consideration in protocol modification. After IV antibiotics are administered for a period of at least 24 hours, a regimen of oral antibiotics will be continued for a total treatment length of 10 days. Acceptable oral regimens should be based on *in vitro* activity against aerobic and anaerobic Gram-negative bacteria known to cause appendicitis, and practical experience with oral antibiotic regimens used to treat diverticulitis. Preferred oral antibiotic regimens include Moxifloxacin alone, and combinations such as Metronidazole or Clindamycin, for anaerobic bacteria coverage, plus Ciprofloxacin or Levofloxacin, or an oral Cephalosporin for aerobic Gram-negative bacteria coverage. Antibiotics will be prescribed by clinicians and procured by patient as per usual clinical care.

4.5.1 Discharge Criteria

Beginning after adequate evaluation of a patient following treatment, clinical staff will have the option to discharge the patient if they meet specific criteria:

1. Stable and near normal vital signs appropriate for age;
2. Afebrile;
3. Signs and symptoms controlled with oral analgesics;
4. Patient able to tolerate oral fluids (e.g., water, broth) and medication;
5. Patient and clinician (emergency physician and surgery team agreement) report that discharge is acceptable; and
6. Routine clinical follow-up visit confirmed.

4.5.2 Guidance for Appendectomy in Patients Randomized to Antibiotics

For participants randomized to the antibiotics arm, appendectomy will be recommended when there is:

1. Development of diffuse peritonitis;
2. Development of severe sepsis/septic shock (e.g., systolic BP <90 mmHg, persistent tachycardia >120 after adequate fluid resuscitation and analgesics); and/or
3. Worsening signs and symptoms of appendicitis after 48 hours following the first antibiotics dose.

Absent these criteria, patients will be encouraged to continue with the antibiotics treatment strategy, especially during the first 48 hours of treatment. At any point after initiating the antibiotics strategy, the surgeon and patient can determine that an appendectomy should be performed. When a decision for appendectomy is being considered, the site lead investigator will be notified to determine if either the above criteria are met or, if not, to review the surgeon's and patient's specific reasons for recommending (surgeon) or requesting (patient) appendectomy. Participants in the antibiotics arm who return to any of the study sites during the follow-up period (but after the four-week assessment) will be offered appendectomy or the option of another attempt at antibiotics but will not be re-randomized.

All participants will be encouraged to return to the hospital or clinic site if they have recurrent signs and symptoms of appendicitis after the four-week assessment and encouraged to undergo repeat diagnostic imaging to detect recurrent appendicitis.

4.6 Appendectomy Arm

All patients randomized to appendectomy will receive one dose of antibiotics per currently accepted standards described in Section 4.5 when diagnosis is confirmed in the ED. Patients may also receive preoperative antibiotics per hospital standards for surgical infection prevention bundle.

Appendectomy will be performed by an open or laparoscopic approach, depending on patient and surgeon preference.

4.7 Discharge Instructions

The same criteria for discharge will be applied to the antibiotics group and the appendectomy group (Section 4.5.1) including standard discharge instructions and return precautions, telephone or in-person appointments for usual clinical care follow-up (one to three weeks after discharge), and contact information for the study coordinator and surgeon investigator at that site.

5.0 Study Schedule, Withdrawals, Call Triggers, and Compensation

5.1 Study Schedule Overview

Consenting participants will be asked to complete research assessments on the topics and at the time points described in Table 2. Site research coordinators (RCs) will oversee the completion of the Baseline Assessment in-person and will also contact participants by phone to complete the Week 1 and Week 2 Assessments. Participants will then be contacted by phone, mail, or email by the UW Survey Center to complete the Week 4 Assessment, Quarterly Assessments for the first year, and Biannual Assessments in the second year after the participant's initial ED presentation.

Table 2. Participant Assessment Schedule.

Item	Baseline	Follow-Up Time Point								
		First 4 Weeks			Month					
		1	2	4	3	6	9	12	18	24
Patient Point of Contact	Site RC	Site RC		Survey Center (Site RC as backup)						
Contact Information	x	x	x	x	x	x	x	x	x	x
EQ-5D[20]	x			x	x	x	x	x	x	x
10-PROMIS Global Health Short Form[21]	x			x	x			x	x	x