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A Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

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	Treatment options

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A Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

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3 Dr. Davidson affirms that the manuscript is an honest, accurate, and transparent account
4 of the study being reported; that no important aspects of the study have been omitted;
5 and that any discrepancies from the study as planned (and, if relevant, registered) have
6 been explained. We have read and understood BMJ policy on declaration of interests
7 and declare that we have no competing interests.
8

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11

12 **ABSTRACT**

13 **Introduction:** Several European studies suggest that patients with uncomplicated
14 appendicitis can be treated safely with antibiotics. A minority of patients eventually
15 undergo appendectomy within a year, with 10-15% failing to respond in the initial period
16 and a similar proportion with suspected recurrent episodes requiring appendectomy.
17 Nearly all patients with uncomplicated appendicitis in the United States (US) are still
18 treated with surgery. A rigorous comparative effectiveness trial in the US that is
19 sufficiently large and pragmatic to incorporate usual variations in care and measures the
20 patient experience is needed to determine if antibiotics are as good as appendectomy.
21

22 **Objectives:** The Comparing Outcomes of Antibiotic Drugs and Appendectomy (CODA)
23 trial for acute uncomplicated appendicitis (AUA) aims to determine if the antibiotic
24 treatment strategy is non-inferior to appendectomy.

25 **Methods/Analysis:** CODA is a randomized, pragmatic non-inferiority trial that aims to
26 recruit 1552 English and Spanish speaking adults with imaging-confirmed AUA.
27 Participants are randomized to appendectomy or 10 days of antibiotics (including an
28 option for complete outpatient therapy). A total of 500 patients who decline
29 randomization but consent to follow-up will be included in a parallel observational
30 cohort. The primary analytic outcome is QoL (measured by the EuroQol five dimension
31 [EQ-5D] index) at four weeks. Clinical adverse events, rate of eventual appendectomy,
32 decisional regret, return to work/school, work productivity, and healthcare utilization will
33 be compared. Planned exploratory analyses will identify subpopulations that may have a
34 differential risk of eventual appendectomy in the antibiotic treatment arm.
35

36 **Conclusion:** CODA will provide evidence to determine if treating AUA with antibiotics is
37 not worse than appendectomy from the patient perspective. By allowing for the full
38 spectrum of usual clinical care within a pragmatic trial framework and by examining a
39 broad range of PROs and clinical outcomes, the results are intended to inform decision-
40 making for treating this common condition.
41

42 **Strengths and Limitations of this Study:**

- 43 • CODA is a randomized, pragmatic, multi-site non-inferiority trial that aims to
44 determine if antibiotics are as good as appendectomy in treating acute
45 uncomplicated appendicitis.
- 46 • The primary analytic outcome is quality of life at four weeks and clinical adverse
47 events, appendicitis signs and symptoms, rate of eventual appendectomy, anxiety,
48 decisional regret, return to work/school, work productivity, and healthcare utilization
49 will also be compared. Exploratory analyses will identify subpopulations at higher risk
50 of eventual appendectomy in the antibiotic treatment arm.
- 51 • Stakeholders including patients, clinicians, and leaders in healthcare and industry
52 provided input that influenced the study design, protocol, patient-facing study
53 materials, and clinical and patient reported outcomes.
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- CODA was designed to inform patient and clinician decision-making; study results will be readily generalizable as CODA takes places in diverse study sites recruiting a heterogeneous patient population.
- CODA is limited to adults.

Ethics and Dissemination: This trial was approved by the University of Washington's Human Subjects Division on April 21, 2016. The University of Washington serves as the IRB of record for the following study sites: University of Washington Medical Center, Harborview Medical Center, Virginia Mason Medical Center, and Madigan Army Medical Center. Western IRB is the overseeing IRB for Swedish-First Hill (approved July 8, 2016) and Providence Regional Medical Center (approved July 1, 2016). UCLA-Olive View (approved June 12, 2016) and UCLA-Harbor (approved March 4, 2016) are both regulated by their respective institutional IRBs.

Trial Registration: Clinicaltrials.org registered on: June 10, 2016 (NCT02800785)

INTRODUCTION

Acute appendicitis is the most common reason for an urgent abdominal operation, with a lifetime incidence of 7-15%.¹ Each year nearly 300,000 Americans are hospitalized for appendicitis at a cost of \$7.8 billion.^{2,3} While appendectomy has been the treatment of choice for 120 years, the successful use of antibiotics was reported both in a series of over 500 patients treated with Streptomycin in the 1950s and later in submariners who did not have access to surgical teams.^{4,5} As anesthesia and surgical safety improved throughout the 20th century, the antibiotics treatment strategy was relegated to patients with complicated disease (e.g., phlegmon) severe enough that surgeons felt there was a higher risk for surgical complications or the need for a more extensive procedure.

Based on these successes with an antibiotic strategy, in the 1990s European investigators began challenging the notion that surgery was the best approach to treat acute uncomplicated appendicitis with a series of randomized trials comparing antibiotics and appendectomy.^{4,6-10} A recent meta-analysis of six randomized trials including 1,724 randomized adult patients concluded there was a high level of efficacy (91% success in the short term with 71% appendectomy free by 1 year), less pain and a quicker return to work in the antibiotic arm.¹¹ The largest, most rigorous and recent trial found a lower rate of complications in the antibiotics group when compared to those having open surgical procedures.¹² However, in addition to the potential for recurrence of appendicitis, a small proportion of patients treated with antibiotics likely had a neoplasm that would have been incidentally identified had they undergone appendectomy. A recent meta-analysis reported incidental appendiceal neoplasm in 5 of 843 (0.59%) patients undergoing surgery.¹¹ The meta-analysis overall concluded that laparoscopic appendectomy remains the usual treatment for appendicitis and there is a "poor evidence base overall with numerous areas of bias", limiting the use of the data for decision making.

The limitations of the existing data regarding antibiotics as a primary treatment for acute uncomplicated appendicitis have been systematically reviewed.¹³ Most studies had small sample sizes; several did not have standardized imaging for diagnosing appendicitis leading to inclusion of patients with complicated appendicitis and patients without appendicitis; inexact and subjective outcome definitions and operation/re-operation criteria were utilized; there were limited or no laparoscopic options for surgery, and in some cases, inadequate antibiotic regimens allowed; and most had short follow-up (no studies reported following patients beyond one year).¹³ While some studies evaluated outcomes including general pain scores and use of narcotic pain medication,

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3 no study used a validated patient-reported outcome (PRO) tool to measure the patient's
4 experience in a standardized fashion. Other important outcomes to patients such as
5 impact on work and school productivity, lingering symptoms, decisional regret, and
6 healthcare burden (such as emergency room care or future imaging) were not included
7 in prior studies. Furthermore, prior studies regimented care in ways that are not
8 consistent with care in the United States (US), such as requiring several days of in-
9 hospital convalescence. These limitations may explain the infrequent use of antibiotics
10 as the primary treatment for acute uncomplicated appendicitis in the US.¹⁴

11
12 In addition to the need to address these limitations, there are additional,
13 unresolved questions that make a larger, more definitive study of this treatment question
14 important. First, there may be important subgroups of people with acute uncomplicated
15 appendicitis who experience the treatment differentially. These might include older
16 patients, who are at higher risk for surgical complications, those with possible
17 appendiceal perforation detected on imaging (without abscess or phlegmon that would
18 classify them as having complicated appendicitis), or those with an appendicolith. The
19 association between appendicolith and worse outcomes with antibiotics is unclear.
20 Appendicoliths are found in up to 20% of appendicitis cases; a similar proportion is also
21 described in autopsy studies of normal appendices.¹⁵ In several pediatric studies and at
22 least one adult study, appendicolith seemed to be associated with antibiotic failure;
23 however, since many trials did not include standardized imaging or "failure" criteria for
24 requiring appendectomy following antibiotic therapy for appendicitis, it is unclear if the
25 presence of an appendicolith actually confers a greater risk.^{16 17} Radiographic findings of
26 appendiceal perforation is another area of controversy. The use of radiologic imaging to
27 accurately determine perforation is limited; in prior studies, patients with perforation were
28 likely to have been inadvertently included due to a lack of imaging.¹⁸ Finally, the
29 European studies also mandated the use of inpatient antibiotics at a time when there
30 was a growing use of outpatient antibiotic regimens for similar conditions, such as acute
31 diverticulitis.¹⁹⁻²¹ A recently completed, pilot randomized trial in the US found that 14 of
32 15 adults randomized to antibiotics could successfully be discharged from the
33 emergency department (ED) and receive all their care as outpatients, resolving their
34 symptoms of acute appendicitis.²² One of the remaining questions is whether this total
35 outpatient approach to antibiotics would be as good as appendectomy in usual practice.

36
37 Given these evidence gaps it remains to be determined if, from the patient's
38 perspective, the antibiotic treatment approach is similar, definitively not worse, and
39 perhaps even superior than the standard treatment of appendectomy. The Comparing
40 Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial was designed to address
41 this question and inform decision-making, focusing on commonly used surgical
42 strategies and a range of antibiotic strategies, including total outpatient therapy, across a
43 broad range of practice environments and a heterogeneous group of patients. These
44 questions provide strong motivation for a pragmatic trial of antibiotics for acute
45 appendicitis.
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48 49 **TRIAL DESIGN**

50 **Stakeholder Input in Design, Informed Consent, and Protocol**

51
52 A central feature of the CODA trial is its engagement of stakeholders in study
53 conception, design, and implementation of the trial.²³ The Stakeholder Coordinating
54 Center (SCC), established as a formal core within the study infrastructure, facilitates all
55 engagement activities. The SCC engages representatives from the patient population of
56 interest (those at risk for or who have had acute uncomplicated appendicitis), clinicians
57 who are involved in appendicitis treatment (including emergency physicians, nurses, and
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3 surgeons), leaders of professional societies (American College of Surgeons and
4 American College of Emergency Physicians), representatives of Accountable Care
5 Organizations, policy-makers, insurers and payers, researchers, and leaders from large,
6 self-insured employers. Specific areas of protocol development informed by the SCC
7 included selecting primary and secondary outcomes. In addition to the routine clinical
8 metrics that are assessed in any study of acute uncomplicated appendicitis treatment,
9 other outcome measures important to patients (anxiety, quality of life, time away from
10 work, out of pocket expenses) and employers (time away from work and productivity at
11 work) were included. Stakeholder input was particularly helpful in determining the
12 primary analytic outcome, helping weigh the prior evidence showing no difference in
13 rates of complications with an outcome metric that would “sum up” the impact of both
14 treatments on the care experience of patients.
15

16 Because appendectomy was considered the standard and nearly universal
17 therapy in the US, advisors recommended a study that considered the non-inferiority of
18 the antibiotics-first strategy. As one advisor said, “the burden of proof is on the
19 antibiotics treatment approach to demonstrate that it is as good as appendectomy” (or
20 not inferior by more than a small margin). Advisors also favored a non-inferiority
21 framework because the larger size required for this design would also allow for multiple
22 planned sub-group analyses for patient groups of interest and the possibility that
23 superiority of the PRO measure might be demonstrated. Lastly, advisors suggested a
24 parallel observational cohort to assess for potential selection bias for patients who
25 declined randomization.
26

27 Patient advisors with an experience of incidentally identified neoplasm at the time
28 of appendectomy helped modify the inclusion criteria (excluding all patients with
29 suggestion of mass of the appendix on imaging), consent form (adding language to
30 make sure that patients were informed about this risk, estimated to be 0.6%), and
31 directed a change in the protocol (those with lingering symptoms in the antibiotics group
32 would be directed to follow-up visits and usual care diagnostic evaluations to rule out a
33 neoplasm).
34

35 36 **Study Aims and Hypothesis**

37 The aims of the study are to compare PROs and clinical outcomes in patients
38 randomized to antibiotics or appendectomy. We hypothesize that antibiotics are non-
39 inferior to appendectomy for PROs and that there are subgroups with better outcomes
40 (clinical and patient-reported) with either treatment. A second set of aims is to perform
41 subpopulation analyses for patients with appendicolith, imaging correlates that may
42 indicate higher risk of antibiotic failure, advanced age, sex, comorbid conditions, and
43 insurance status.
44

45 **Study population**

46 The study population includes consecutively presenting English or Spanish speaking
47 adults (age ≥ 18 years) with clinically suspected and imaging-confirmed acute
48 uncomplicated appendicitis who present at study site hospital EDs in several states.
49

50 *Exclusion Criteria*

- 51
- 52 • Inability to participate in follow-up (i.e., incarcerated, travel without access to
53 phone, email)
 - 54 • Contraindication to one of the study treatment arms:
 - 55 ○ Septic shock
 - 56 ○ Phlegmon for which surgery would not be recommended or diffuse
57 peritonitis for which antibiotics alone would not be recommended
 - 58
 - 59
 - 60

- Imaging findings of complicated appendicitis (walled off abscess and/or free air)
- Appendiceal soft-tissue mass concerning for malignancy
- Other conditions precluding study involvement:
 - Uncompensated liver failure
 - Inflammatory bowel disease requiring active medical treatment (e.g., Crohn's, ulcerative colitis)
 - Pregnancy or expectation of becoming pregnant in the 30 days following baseline/screening.
 - Surgical implant (e.g., left ventricular assist device, peritoneal dialysis)
 - Malignancy requiring active treatment (e.g., chemotherapy)
 - Immunodeficiency (e.g., AIDS)
 - Another infection currently treated with systemic antibiotics
 - Concurrent illness that would otherwise mandate inpatient hospitalization
 - Severe allergy or reaction to all proposed antibiotics
 - Abdominal or pelvic surgery in the past 30 days

Of note, patients with radiologic diagnosis of appendicolith and/or imaging concerning for appendiceal perforation or phlegmon are included if they do not meet the above exclusion criteria and are otherwise eligible.

Recruitment

All patients presenting to the ED with concern for appendicitis are screened by study coordinators (seven days a week, at least 18 hours per day) based on alerts from clinicians, staff, and screening of ED logs. Patients are identified as potential study candidates based on eligibility criteria collected as part of standard care, including confirmatory diagnostic imaging (CT, US, and/or MRI). A research coordinator and a representative from the clinical team confirm the patient's eligibility for the study. A research team member approaches all eligible patients and invites them to view a less than 10-minute standardized informed decision-making video providing standard information about appendicitis and the different treatment options (offered in English and Spanish versions, <https://www.youtube.com/playlist?list=PLQUQ6jdR0MPaq-a8CvSdhVwnuYzNKF9tu>).

Participants who decline randomization are asked to participate in the observational cohort (with similar baseline and follow-up measures as participants in the RCT). All patients are asked for permission to be followed through passive electronic medical record (EMR) review.

Participant Follow Up Assessment:

Participants are contacted 24-48 hours after discharge by a member of the research team to answer any questions about the study and review the survey protocol (see Table 1. Participant Assessment Schedule). Participants are then contacted by phone by site research coordinators one and two weeks after enrollment for study assessments. Data collected through the two week assessment are entered by site research coordinators into a REDCap database, which is managed by the University of Washington (UW) data coordinating center (DCC).²⁴ Starting with the Week 4 Assessment, corresponding to our primary endpoint assessment, participants are contacted by phone, mail, or email by the UWUW Survey Center to complete the remaining study assessments (at 3, 6, 9, 12, 18 and 24 month surveys).. The UW Survey Center uses the DatStat survey platform (DatStat, Inc., Seattle, WA) to create individualized outreach plans that optimize survey completion rates. Outreach methods

are modified to accommodate a participant's preferred mode of contact (email, mail, phone) as well as time of day for contact (if by phone). If a participant requests to speak with a medical provider or has concerning medical symptoms reported to the research team, the clinical team via the surgical site lead is contacted to call the participant for further follow up.

Table 1. Participant Assessment Schedule.

Item	Baseline	Follow-Up Time Point								
		First 4 Weeks			Month					
		1	2	4	3	6	9	12	18	24
Participant Point of Contact	Site Research Team (RT)	Site RT		Survey Center						
Contact Information	X	X	X	X	X	X	X	X	X	X
EQ-5D ²⁵	X			X	X	X	X	X	X	X
10-PROMIS Global Health Short Form ²⁶	X			X	X			X	X	X
PROMIS-Pain Intensity	X	X	X							
Symptom Onset	X									
Additional Demographics*	X									
Treatment Satisfaction/Expectation	X			X	X**					
Gastrointestinal Quality of Life (GIQLI) ²⁷				X	X			X	X	X
Healthcare Utilization		X	X	X	X	X	X	X	X	X
Signs & Symptoms of Appendicitis		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Decision Regret Scale ²⁸				X	X			X		
Major Life Changes				X	X	X	X	X	X	X
Work Productivity Index		X	X	X	X					
Return to Work Information		X	X	X	X**					
Medication Use		X	X	X	X**					
Treatment Strategy Change		X	X	X						

*Includes the following topics: Demographics & Gender Identity, Caregiver Role, Instrumental Support, Employment/Student Status, Income, Pain Catastrophizing, Health Literacy, Social Support, Confidence in Treatment Success, Trust in Healthcare

**Only asked if the one month results have not normalized

The DCC performs early quality assurance checks by running REDCap data quality reports. These reports identify missing values for required fields, incorrect data type, range checks, outliers, hidden fields that contain values, and multiple choice fields with invalid values. Values that need to be corrected are brought to the attention of the research staff at that site.

Study Arms

Antibiotics Therapy Arm

Patients in the antibiotics treatment arm receive a minimum of 24 hours of treatment using an intravenous (IV) antibiotic formulation (administered in q8, q12, or q24 hour regimens) followed by oral antibiotics for a total of a 10-day antibiotic course. Patients are offered a treatment regimen of antibiotics based on guidelines published jointly by the Surgical Infection Society (SIS) and the Infectious Disease Society of America (IDSA) for intravenous antibiotics²⁹ and oral antibiotics based on *in vitro* activity against aerobic and anaerobic Gram-negative bacteria, practical experience with oral antibiotic regimens used to treat diverticulitis, and IDSA/SIS guidelines. The first dose of antibiotics is given in the ED at the time of diagnosis of appendicitis and a total outpatient regimen of antibiotics is an option for patients meeting ED discharge criteria. Antibiotics are procured from the pharmacy by the patient as per usual clinical care.

Appendectomy is recommended only if there is development of diffuse peritonitis, development of septic shock, and/or worsening signs and symptoms of appendicitis after 48 hours. The decision to perform an appendectomy in participants randomized to antibiotics is made by the treating surgeon after consultation with the study clinical research lead to confirm that the above criteria have been satisfied.

Standard discharge criteria are applied to those treated in the ED and those who are admitted, and the criteria include tolerance of liquids, adequate pain control, and improving clinical condition. All participants are contacted at 24-48 hours by the research coordinator to review the study protocol for follow-up assessments.

Follow-up with the clinical team is per usual care at each institution. Participants in the antibiotics arm who return to any of the study sites during the follow-up period with recurrent appendicitis are not re-randomized but are offered the choice of either appendectomy or another antibiotic course, if treating surgeon agrees their recurrence can be treated with either option.

Appendectomy Therapy Arm

All patients randomized to appendectomy receive preoperative antibiotics per hospital standards for surgical infection prevention protocols. Appendectomy is performed by an open or laparoscopic approach, depending on patient and surgeon preference.

Blinding and Randomization

This is an un-blinded study as patients will know if they were randomized to appendectomy or antibiotics. A separate data coordinating center (DCC) at the University of Washington (UW) generates and maintains randomization lists for each practice site. Using block randomization optimizes the chances of equal numbers of subjects being randomized to each treatment arm and that treatment is balanced at periodic enrollment intervals. Randomization is further stratified by the presence of appendicolith. All other subgroups of interest will be sufficiently large such that the risk of a meaningful imbalance in treatment groups by chance is unlikely. A web-based portal provides the randomized treatment assignment.

Outcomes and Measures

The primary outcome for the CODA trial is the EQ-5D index reported four weeks after randomization. Important clinical outcomes include major complications and resolution of symptoms by four weeks, eventual appendectomy (due to initial antibiotic

treatment failure as well as due to recurrent appendicitis), pain, narcotic use, recurrent episodes of appendicitis, ED visits for abdominal pain/repeat imaging, need for more complicated surgical procedure including laparoscopic converted to open appendectomy and ileocecectomy, rates of perforation, and rates of future small bowel obstructions and hernia development through two years. Complications in both treatment groups are tracked and adjudicated by an independent safety monitor to determine their relation to the disease and treatment. Secondary PROs include a measure of decisional regret, anxiety, additional QoL measures (PROMIS-Global, Gastrointestinal Quality of Life Index (GIQLI)), days missed from work or school, time in healthcare, measures of caregiver burden, and out-of-pocket expenses.

Sample Size

The sample size was calculated based on the difference in EQ-5D between the two treatment interventions. EQ-5D. The EQ-5D QoL index ranges from 0 (worst QoL) to 1 (highest QoL), where anchor-based methods have shown that the minimally clinically important difference ranges 5%-10%.³⁰ Based on data from a prior study of appendectomy with EQ-5D scores at 12 weeks,³¹ we estimate that the average EQ-5D for the participants randomized to appendectomy will be 0.90 with a standard deviation of 0.12. In order to assess QoL differences between interventions, a total of 1,552 patients will be enrolled, assuming a 90% follow-up at 4-weeks. This will give the study very high power (>99%) to rule out an EQ-5D difference between groups as small as 5% (if treatment differences of 0 to 2% are observed) and 80% power if a treatment difference of 3% is observed.²²

Table 2. Statistical power to declare non-inferiority on patient-reported quality of life, overall and by subgroup (Non-inferiority Margin, M = -5%, one-sided alpha=0.025).

Treatment Difference, Δ	Overall	Subgroups		
	N=1552	N=250	N=400	N=500
-3%	82.6%	-	-	-
-2%	99.4%	-	57.1%	67.9%
-1%	100%	62.4%	83.8%	91.4%
0%	100%	83.0%	96.4%	98.8%

Based on pilot data, stakeholder engagement, and we estimate a randomization rate of 30% of all potential patients. Based on current appendectomy volume at the hospitals participating in the trial, recruitment is planned for three years with potential for extension through four years.

Statistical Analysis

We will assess the EQ-5D at four weeks, using a linear regression model that adjusts for an indicator of randomized treatment group assignment and for all factors used to stratify randomization (i.e., recruitment site, presence of appendicolith). As recommended by the US Food and Drug Administration guidelines on clinical trial design, the estimated treatment effect and 97.5% one-sided confidence interval (CI) will be compared to the non-inferiority margin (M = -5%).³²⁻³⁵ We will conclude that antibiotics are non-inferior to appendectomy if the entire 97.5% one-sided CI is greater than M, as in example scenario A (Figure 1). This is equivalent to a one-sided (alpha=0.025) test of the null hypothesis $H_0: \Delta \leq -5\%$, for which Δ represents the

1
2
3 difference in mean EQ-5D at 4-weeks comparing antibiotics-first to appendectomy-first
4 treatment assignment. If the null hypothesis of $H_0: \Delta \leq -5\%$ is rejected at the final
5 evaluation, then we will conduct a test of superiority to determine the level of statistical
6 evidence supporting an alternative hypothesis $H_A: \Delta > 0\%$ (i.e., scenario B of Figure 1).
7

8 Important clinical endpoints (30-day major complications, days until resolution of
9 symptoms, rates of perforated appendicitis, extent of operation and surgical
10 complications, complications associated with antibiotics, hospital days, number of days
11 using antibiotics beyond the initial treatment, clinic visits, and caregiver/patient “time in
12 healthcare”) will also be compared between ITT groups using regression models
13 appropriate to each endpoint (e.g., linear, logistic, Poisson, or Cox proportional hazards
14 regression models), along with a similar non-inferiority framework.
15

16 17 **Secondary Analyses**

18 We aim to include a heterogeneous population of patients and healthcare
19 settings and plan to explore differences in treatment outcomes across subgroups of
20 interest, including those with appendicolith, people with specific imaging findings
21 including possible appendiceal perforation, those in different age groups (18-64 or ≥ 65),
22 sex, and those whose outcomes may vary due to differences in work and insurance
23 status, comorbidities, or social support. We will delegate evaluate difference in treatment
24 effectiveness based on modality of receipt of antibiotics (all outpatient vs
25 inpatient/outpatient). We will separately assess treatment effect heterogeneity by adding
26 to the primary outcome model an interaction term between the categorical subgroup
27 variable of interest and the indicator of treatment. We will use a global likelihood ratio
28 test to examine if the treatment effect differs between key subgroups of interest.
29

30 An intention-to-treat (ITT) approach will be applied in the primary analysis. We
31 will conduct a secondary as-treated analysis of the primary outcome measure that
32 appropriately accounts for patient- or provider-level characteristics found to be
33 differentially represented among patients who start in the antibiotics arm and who
34 undergo appendectomy before 24 hours of treatment, or patients who are randomized to
35 appendectomy but refuse the procedure and continue on antibiotics. We will consider a
36 two-stage approach for this as-treated analysis: 1) to identify subgroups that are likely to
37 require appendectomy and therefore should not be considered good candidates for
38 treatment with antibiotics as primary treatment strategy, and; 2) to estimate the complier
39 average causal effect (CACE), which seeks to compare the outcomes of patients treated
40 successfully in the antibiotic treatment arm (i.e., did not ultimately have surgery) with
41 patients randomized to the appendectomy arm who are similar in their expected
42 compliance to assigned treatment.³⁶⁻³⁸ We will use a maximum likelihood mixture
43 modeling approach to identify the optimal comparison group from the control arm for
44 observed compliers in the intervention arm. Secondary analyses of the primary outcome
45 measures will include examining the entire trajectory of EQ-5D QoL measurements for
46 each patient using linear mixed effects models for longitudinal data.³⁹ Lastly, a
47 composite outcome metric (symptom resolution without complication) was used in the
48 recently completed pilot trial and will be included as an exploratory measure.²² Because
49 the composite outcome includes only clinical domains, and is relevant to both treatment
50 groups, this may be a helpful measure for clinicians considering the two treatments.
51
52

53 **Data Safety and Monitoring**

54 *Event Reporting:*

55 Death, life threatening events and rehospitalization (other than for treatment of
56 appendicitis) are classified as SAEs. Morbidity events (using modified definitions from
57 NSQIP to accommodate non-operative care) are considered AEs. Adverse events
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(AEs), serious adverse events (SAEs) and appendectomy after starting antibiotic treatment are identified through 3 approaches; EMR review, patient surveys and through ad hoc reporting by any research or care team member. All SAEs are adjudicated by an independent safety monitor. SAEs and AEs are reviewed by the DSMB biannually (with the exception of death which is reported to the DSMB within 24-hours). An independent Data and Safety Monitoring Board (DSMB) reviews the accruing data to: 1) ensure that study conduct, enrollment, and patient follow-up is adequate; 2) ensure that there are no serious safety concerns; and 3) assess evidence related to patient-reported QoL. The analysis of accruing data is completed by the DCC and interim analysis is presented to the DSMB with the primary goal of monitoring safety outcomes by randomization group. Interim monitoring for SAE and AE will focus on the first four weeks of follow-up. The DSMB will conduct interim analyses at 12, 24, and 36 months.

The CODA trial does not include a stopping rule if non-inferiority is met before complete accrual or if it is determined that non-inferiority cannot be demonstrated in interim analyses. We are not employing a stopping rule because there are important secondary outcomes (e.g rate of eventual appendectomy, complications, subgroup analysis) and understudied subgroups that require full enrollment.

DISCUSSION

Prior trials randomizing patients with acute uncomplicated appendicitis to antibiotics compared to appendectomy focused on disease cure, with the primary outcome being the rate of appendectomy among antibiotic-treated participants. Previous studies of more than 800 participants randomized to antibiotics suggested that the treatment did not increase the rate of complications and offered as high as a 75% chance of avoiding appendectomy within a year.^{6-9 12 41} What remains to be evaluated is the comparative effectiveness of the two candidate treatments based on a comprehensive assessment of impact, including the full range of clinical outcomes and PROs that matter most to patients. CODA's pragmatic design aims to evaluate antibiotics in a heterogeneous population and practice settings in a large randomized trial, with a parallel observational cohort to assess selection bias. One of the greatest novelties of the CODA trial is its patient centeredness, demonstrated both by the engagement of patients and other stakeholders as partners in selecting the topic, designing the proposal, developing the protocol and overseeing operations, as well as in the selection of a QoL endpoint for the primary analysis.

CODA was designed to directly inform patient and clinician decision-making in the community and several pragmatic features were added to make sure it accounted for the diverse aspects of the population, practice settings, and practices in the US. As a pragmatic trial, CODA has limited exclusion criteria and incorporates the many ways clinical care is delivered across sites of practice. The protocol allows patients in either study arm to leave the healthcare setting as soon as standard discharge criteria are met, including the possibility of completely outpatient care. CODA takes place in diverse study sites (academic, private, public, community, and county hospitals) with patients from a wide range of demographic and socioeconomic characteristics, including both Spanish and English speakers. This enhances the generalizability of the findings, but may compromise study fidelity if patients in any one group have differential treatment preferences or prove more difficult to contact for follow-up. A downside to this approach is that by including almost all patients (including those with appendicolith who may be at higher risk of antibiotic "failure") and those undergoing total outpatient antibiotics (which clinicians have less experience with) there is a risk of subgroups with very different

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3 outcomes from the broader population and a skewing of the average study results. Using
4 Thorpe's PRECIS rubric for pragmatic trials, the proposed study is considered highly
5 pragmatic, intended to improve the generalization and precision of decision-making
6 beyond the prior randomized studies.⁴²
7

8 The results from the European trials of antibiotics have not significantly changed
9 care delivery in the US and have been met with resistance, in part due to the evidence
10 gaps cited earlier and concern about the fate of patients with recurrent disease.⁴³
11 American patients may also have different expectations and resources that influence
12 perception of treatment success and satisfaction with treatments. One particular protocol
13 component of the European trials that may make them less applicable to the US
14 experience is that prior studies all required an in-hospital convalescence for a fixed
15 period of time for both treatment arms that is double the length of stay that the average
16 US patient experiences. CODA builds on the successful experience of emergency
17 medicine clinicians to manage patients with potentially serious infections as outpatients
18 using risk-stratification and long-acting parenteral antibiotics (e.g., diverticulitis) and its
19 effectiveness will be tested in different practice settings and populations. This novel
20 treatment alternative offers avoidance of hospital admission and may substantially
21 reduce costs compared to surgical treatment,
22

23 Stakeholder input is a key component of the emerging field of patient-centered
24 outcomes research. However, including several types of stakeholders (patients,
25 physicians, payers, and purchasers) does not always result in consensus. The selection
26 of an appropriate analytic outcome for the trial was an example. While prior studies
27 focused on clinical outcome (e.g., rates of appendectomy and surgical complications),
28 patient advisors recognized that these outcome measures are specific to only one
29 treatment arm (and to people treated with antibiotics who proceed to appendectomy)
30 and that standardized measurements of quality of life would be applicable to both and
31 had yet to be rigorously assessed. The EQ-5D has been used in prior studies of
32 appendectomy, but never in comparisons of these two treatments.³¹ Using the EQ-5D as
33 a primary outcome measure was highly relevant to many, but not all, patients. There is a
34 possibility that the primary analytic outcome analysis (non-inferiority of the EQ-5D) could
35 be positive, but other outcome domains might not be aligned. For this reason, multiple
36 secondary analyses and exploratory endpoints have been selected a priori. Evidence in
37 the field of decision-making suggests that patients want information on multiple domains,
38 but we recognize that multiple outcome domains may also add confusion to
39 interpretation of results and implementation in future practice.
40

41 As in all trials, patients are not required to stay in the treatment arms they are
42 assigned to (non-adherence or crossover); for example, select patients in the antibiotics
43 arm might not be willing to receive 24 hours of antibiotics and opt for an appendectomy
44 despite not meeting clinical recommendations for antibiotic arm treatment failure, or
45 patients randomized to appendectomy might refuse surgery. While the main analytic
46 approach is an intention to treat framework, careful as-treated and secondary data
47 analyses may be helpful in accounting for such non-adherence/crossover.⁴⁴ Detry
48 recommends both an ITT and a careful as-treated analysis to address crossovers in
49 non-inferiority trials where non-adherence or crossover is present.⁴⁵ A simple as-treated
50 analysis is problematic because of potential differences in demographic or clinical
51 characteristics that introduce bias in as-treated group comparisons. Our analytic
52 approach proposed involves a two-stage as-treated analysis and potentially will yield
53 conclusions that differ from ITT analysis. However, the ITT results will be considered the
54 primary analysis and are robustly valid since they only depend on randomization and do
55 not depend on model assumptions required for observational comparisons.⁴⁵
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CODA began recruitment in the Summer/Fall of 2016 and now involves eight hospitals in Washington and California with two hospitals planned to begin recruitment in 2017. It is possible that not all clinical sites will continue to contribute patients throughout the entire recruitment period (projected to be 3-4 years). Sub-studies and ancillary studies are being proposed to focus on biomarkers, economic analysis, longer-term results, and other predictors of outcome.

In conclusion, the CODA trial was designed to address critical knowledge gaps related to the treatment of appendicitis with antibiotics compared with appendectomy. CODA's stakeholder-informed design and operations, pragmatic design, and inclusion of an innovative approach to outpatient antibiotics aim to inform choices in care for this common condition, and planned subgroup analyses allow for improved decision-making.

Contributor statement:

DRF conceived of the study and is the primary grant holder. GHD, DRF, DAT, LGK, DCL, AK, SDS, BAC, PJH, APE, GJM initiated the study design. DAT, LGK, DCL, BJB, FF, SDS, AK, EMW, BAC, SEM, PJH, APE, DAD, AHK, HLE, JTY, KAM, ICD, KSC, KMM, BCT, CSF, DJS, RCT, EOL, AKS, and GJM supported protocol development, refinement, and implementation as directed by GHD and DRF. BAC, SEM, PJH provided statistical expertise in clinical trial design and SEM is conducting the primary statistical analysis. DRF, DAT, LGK, DCL, BJB, FF, SDS, AK, EMW, BAC, SEM, PJH, APE, DAD, AHK, HLE, JTY, KAM, ICD, KSC, KMM, BCT, CSF, DJS, RCT, EOL, AKS, and GJM reviewed and approved the final manuscript as led by GHD.

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Data sharing statement:

No additional data is available at this time.

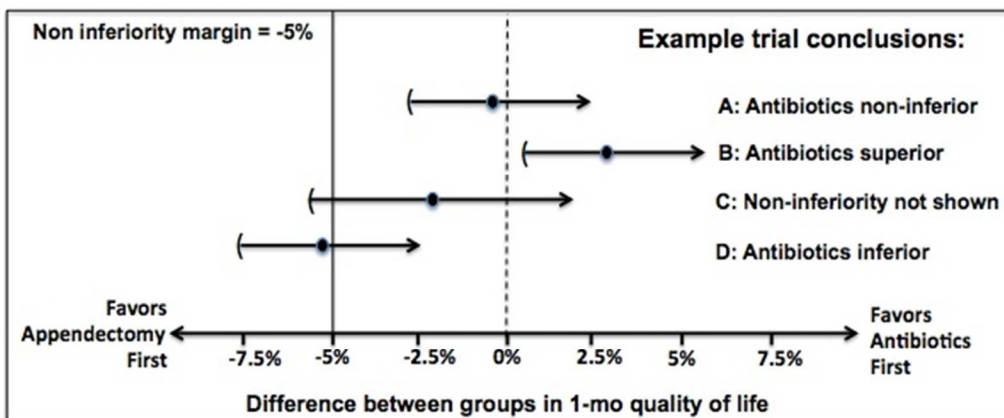
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A Protocol for the Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

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A Protocol for the Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

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3 Dr. Davidson affirms that the manuscript is an honest, accurate, and transparent account
4 of the study being reported; that no important aspects of the study have been omitted;
5 and that any discrepancies from the study as planned (and, if relevant, registered) have
6 been explained. We have read and understood BMJ policy on declaration of interests
7 and declare that we have no competing interests.
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10 Word Count: 5366
11

12 **ABSTRACT**

13 **Introduction:** Several European studies suggest that some patients with appendicitis
14 can be treated safely with antibiotics. A portion of patients eventually undergo
15 appendectomy within a year, with 10-15% failing to respond in the initial period and a
16 similar additional proportion with suspected recurrent episodes requiring appendectomy.
17 Nearly all patients with appendicitis in the United States (US) are still treated with
18 surgery. A rigorous comparative effectiveness trial in the US that is sufficiently large and
19 pragmatic to incorporate usual variations in care and measures the patient experience is
20 needed to determine if antibiotics are as good as appendectomy.
21

22 **Objectives:** The Comparing Outcomes of Antibiotic Drugs and Appendectomy (CODA)
23 trial for acute appendicitis aims to determine if the antibiotic treatment strategy is non-
24 inferior to appendectomy.

25 **Methods/Analysis:** CODA is a randomized, pragmatic non-inferiority trial that aims to
26 recruit 1552 English and Spanish speaking adults with imaging-confirmed appendicitis.
27 Participants are randomized to appendectomy or 10 days of antibiotics (including an
28 option for complete outpatient therapy). A total of 500 patients who decline
29 randomization but consent to follow-up will be included in a parallel observational
30 cohort. The primary analytic outcome is QoL (measured by the EuroQol five dimension
31 [EQ-5D] index) at four weeks. Clinical adverse events, rate of eventual appendectomy,
32 decisional regret, return to work/school, work productivity, and healthcare utilization will
33 be compared. Planned exploratory analyses will identify subpopulations that may have a
34 differential risk of eventual appendectomy in the antibiotic treatment arm.
35

36 **Conclusion:** CODA will provide evidence to determine if treating appendicitis with
37 antibiotics is not worse than appendectomy from the patient perspective. By allowing for
38 the full spectrum of usual clinical care within a pragmatic trial framework and by
39 examining a broad range of PROs and clinical outcomes, the results are intended to
40 inform decision-making for treating this common condition.
41

42 **Strengths and Limitations of this Study:**

- 43 • CODA is a randomized, pragmatic, multi-site non-inferiority trial that aims to
44 determine if antibiotics are as good as appendectomy in treating most cases of acute
45 appendicitis.
- 46 • The primary analytic outcome is quality of life at four weeks and clinical adverse
47 events, appendicitis signs and symptoms, rate of eventual appendectomy, anxiety,
48 decisional regret, return to work/school, work productivity, and healthcare utilization
49 will also be compared. Exploratory analyses will identify subpopulations at higher risk
50 of eventual appendectomy in the antibiotic treatment arm.
- 51 • Stakeholders including patients, clinicians, and leaders in healthcare and industry
52 provided input that influenced the study design, protocol, patient-facing study
53 materials, and clinical and patient reported outcomes.
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- CODA was designed to inform patient and clinician decision-making; study results will be readily generalizable as CODA takes places in diverse study sites recruiting a heterogeneous patient population.
- CODA is limited to adults.

Ethics and Dissemination: This trial was approved by the University of Washington's Human Subjects Division on April 21, 2016 (Version 3.5). The University of Washington serves as the IRB of record for the following study sites: University of Washington Medical Center, Harborview Medical Center, Virginia Mason Medical Center, and Madigan Army Medical Center. Western IRB is the overseeing IRB for Swedish-First Hill (approved July 8, 2016) and Providence Regional Medical Center (approved July 1, 2016). UCLA-Olive View (approved June 12, 2016) and UCLA-Harbor (approved March 4, 2016) are both regulated by their respective institutional IRBs.

Trial Registration: Clinicaltrials.org registered on: June 10, 2016 (NCT02800785)

INTRODUCTION

Acute appendicitis is the most common reason for an urgent abdominal operation, with a lifetime incidence of 7-15%.¹ Each year nearly 300,000 Americans are hospitalized for appendicitis at a cost of \$7.8 billion.^{2,3} While appendectomy has been the treatment of choice for 120 years, the successful use of antibiotics was reported both in a series of over 500 patients treated with Streptomycin in the 1950s and later in submariners who did not have access to surgical teams.^{4,5} As anesthesia and surgical safety improved throughout the 20th century, the antibiotics treatment strategy was relegated to patients with disease severe enough (e.g., phlegmon at the cecum, abscess) that surgeons felt there was a higher risk for surgical complications or the need for a more extensive procedure.

Based on these successes with an antibiotic strategy, in the 1990s European investigators began challenging the notion that surgery was the best approach to treat acute "uncomplicated" appendicitis with a series of randomized trials comparing antibiotics and appendectomy.⁴⁻¹⁰ A recent meta-analysis of six randomized trials including 1,724 randomized adult patients concluded there was a high level of efficacy (91% success in the short term with 71% appendectomy free by 1 year), less pain and a quicker return to work in the antibiotic arm.¹¹ The largest, most rigorous and recent trial found a lower rate of complications in the antibiotics group when compared to those having open surgical procedures.¹² However, in addition to the potential for recurrence of appendicitis, a small proportion of patients treated with antibiotics likely had a neoplasm that would have been incidentally identified had they undergone appendectomy. A recent meta-analysis reported incidental appendiceal neoplasm in 5 of 843 (0.59%) patients undergoing surgery.¹¹ The meta-analysis overall concluded that laparoscopic appendectomy remains the usual treatment for appendicitis and there is a "poor evidence base overall with numerous areas of bias", limiting the use of the data for decision making.

The limitations of the existing data regarding antibiotics as a primary treatment for acute appendicitis have been systematically reviewed.¹³ Most studies had small sample sizes; several did not have standardized imaging for diagnosing appendicitis leading to inclusion of patients who likely had "complicated" appendicitis and patients without appendicitis; inexact and subjective outcome definitions and operation/re-operation criteria were utilized; there were limited or no laparoscopic options for surgery, and in some cases, inadequate antibiotic regimens allowed; and most had short follow-up (no studies reported following patients beyond one year).¹³ While some studies evaluated outcomes including general pain scores and use of narcotic pain medication,

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3 no study used a validated patient-reported outcome (PRO) tool to measure the patient's
4 experience in a standardized fashion. Other important outcomes to patients such as
5 impact on work and school productivity, lingering symptoms, decisional regret, and
6 healthcare burden (such as emergency room care or future imaging) were not included
7 in prior studies. Furthermore, prior studies regimented care in ways that are not
8 consistent with care in the United States (US), such as requiring several days of in-
9 hospital convalescence. These limitations may explain the infrequent use of antibiotics
10 as the primary treatment for appendicitis in the US.¹⁴

11
12 In addition to the need to address these limitations, there are additional,
13 unresolved questions that make a larger, more definitive study of this treatment question
14 important. First, there may be important subgroups of people with acute appendicitis
15 who experience the treatment differentially. These might include older patients, who are
16 at higher risk for surgical complications, those with possible appendiceal perforation
17 detected on imaging, or those with an appendicolith. The association between
18 appendicolith and worse outcomes with antibiotics is unclear. Appendicoliths are found
19 in up to 20% of appendicitis cases; a similar proportion is also described in autopsy
20 studies of normal appendices.¹⁵ In several pediatric studies and at least one adult study,
21 appendicolith seemed to be associated with eventual appendectomy; however, since
22 many trials did not include standardized imaging or criteria for requiring appendectomy
23 following antibiotic therapy for appendicitis, it is unclear if the presence of an
24 appendicolith actually confers a greater risk.^{16 17} There is currently no standard definition
25 of "complicated" disease. In the United States, usual care for appendiceal abscess or
26 pphemon (inflammation so significant that surgeons are concerned for associated
27 surgical morbidity) is antibiotics with consideration for interval appendectomy. Optimal
28 treatment strategies for preoperative radiographic findings of appendiceal perforation is
29 an area of controversy. The use of radiologic imaging to accurately determine
30 perforation is limited; in prior randomized trials, patients with perforation were likely to
31 have been inadvertently included due to a lack of imaging.¹⁸ Finally, the European
32 studies mandated the use of inpatient antibiotics at a time when there was a growing use
33 of outpatient antibiotic regimens for similar conditions, such as acute diverticulitis.¹⁹⁻²¹ A
34 recently completed, pilot randomized trial in the US found that 14 of 15 adults
35 randomized to antibiotics could successfully be discharged from the emergency
36 department (ED) and receive all their care as outpatients, resolving their symptoms of
37 acute appendicitis.²² One of the remaining questions is whether this total outpatient
38 approach to antibiotics would be as good as appendectomy in usual practice.

39
40 Given these evidence gaps it remains to be determined if, from the patient's
41 perspective, the antibiotic treatment approach is similar, definitively not worse, and
42 perhaps even superior than the standard treatment of appendectomy. The Comparing
43 Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial was designed to address
44 this question and inform decision-making, focusing on commonly used surgical
45 strategies and a range of antibiotic strategies, including total outpatient therapy, across a
46 broad range of practice environments and a heterogeneous group of patients. These
47 questions provide strong motivation for a pragmatic trial of antibiotics for acute
48 appendicitis.

51 52 TRIAL DESIGN

53 Stakeholder Input in Design, Informed Consent, and Protocol

54
55 A central feature of the CODA trial is its engagement of stakeholders in study
56 conception, design, and implementation of the trial.²³ The Stakeholder Coordinating
57 Center (SCC), established as a formal core within the study infrastructure, facilitates all
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3 engagement activities. The SCC engages representatives from the patient population of
4 interest (those at risk for or who have had appendicitis), clinicians who are involved in
5 appendicitis treatment (including emergency physicians, nurses, and surgeons), leaders
6 of professional societies (American College of Surgeons and American College of
7 Emergency Physicians), representatives of Accountable Care Organizations, policy-
8 makers, insurers and payers, researchers, and leaders from large, self-insured
9 employers. Specific areas of protocol development informed by the SCC included
10 selecting primary and secondary outcomes. In addition to the routine clinical metrics that
11 are assessed in any study of appendicitis treatment, other outcome measures important
12 to patients (anxiety, quality of life, time away from work, out of pocket expenses) and
13 employers (time away from work and productivity at work) were included. Stakeholder
14 input was particularly helpful in determining the primary analytic outcome, helping weigh
15 the prior evidence showing no difference in rates of complications with an outcome
16 metric that would “sum up” the impact of both treatments on the care experience of
17 patients.
18

19
20 Because appendectomy was considered the standard and nearly universal
21 therapy in the US, advisors recommended a study that considered the non-inferiority of
22 the antibiotics-first strategy. As one advisor said, “the burden of proof is on the
23 antibiotics treatment approach to demonstrate that it is as good as appendectomy” (or
24 not inferior by more than a small margin). Advisors also favored a non-inferiority
25 framework because the larger size required for this design would also allow for multiple
26 planned sub-group analyses for patient groups of interest and the possibility that
27 superiority of the PRO measure might be demonstrated. Lastly, advisors suggested a
28 parallel observational cohort to assess for potential selection bias for patients who
29 declined randomization.
30

31 Patient advisors with an experience of incidentally identified neoplasm at the time
32 of appendectomy helped modify the inclusion criteria (excluding all patients with
33 suggestion of mass of the appendix on imaging), consent form (adding language to
34 make sure that patients were informed about this risk, estimated to be 0.6%), and
35 directed a change in the protocol (those with lingering symptoms in the antibiotics group
36 would be directed to follow-up visits and usual care diagnostic evaluations to rule out a
37 neoplasm).
38

39 **Study Aims and Hypothesis**

40 The aims of the study are to compare PROs and clinical outcomes in patients
41 randomized to antibiotics or appendectomy. We hypothesize that antibiotics are non-
42 inferior to appendectomy for PROs and that there are subgroups with better outcomes
43 (clinical and patient-reported) with either treatment. A second set of aims is to perform
44 subpopulation analyses for patients with appendicolith and imaging correlates that may
45 indicate higher risk of requiring appendectomy following initiation of antibiotic therapy,
46 advanced age, sex, comorbid conditions, and insurance status.
47

48 **Study population**

49 The study population includes consecutively presenting English or Spanish speaking
50 adults (age ≥ 18 years) with clinically suspected and imaging-confirmed acute
51 appendicitis who present at study site hospital EDs in several states.
52

53 *Exclusion Criteria*

- 54
- 55 • Inability to participate in follow-up (i.e., incarcerated, travel without access to
56 phone, email)
- 57 • Contraindication to one of the study treatment arms:
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- Septic shock
- Phlegmon for which surgery would not be recommended or diffuse peritonitis for which antibiotics alone would not be recommended
- Imaging findings of walled off abscess and/or free air
- Appendiceal soft-tissue mass concerning for malignancy
- Other conditions precluding study involvement:
 - Uncompensated liver failure
 - Inflammatory bowel disease requiring active medical treatment (e.g., Crohn's, ulcerative colitis)
 - Pregnancy or expectation of becoming pregnant in the 30 days following baseline/screening.
 - Surgical implant (e.g., left ventricular assist device, peritoneal dialysis)
 - Malignancy requiring active treatment (e.g., chemotherapy)
 - Immunodeficiency (e.g., AIDS)
 - Another infection currently treated with systemic antibiotics
 - Concurrent illness that would otherwise mandate inpatient hospitalization
 - Severe allergy or reaction to all proposed antibiotics
 - Abdominal or pelvic surgery in the past 30 days

Of note, patients with radiologic diagnosis of appendicolith and/or imaging concerning for appendiceal perforation or phlegmon are included if they do not meet the above exclusion criteria and are otherwise eligible.

Recruitment

All patients presenting to the ED with concern for appendicitis are screened by study coordinators (seven days a week, at least 18 hours per day) based on alerts from clinicians, staff, and screening of ED logs. Patients are identified as potential study candidates based on eligibility criteria collected as part of standard care, including confirmatory diagnostic imaging (CT, US, and/or MRI). A research coordinator and a representative from the clinical team confirm the patient's eligibility for the study. A research team member approaches all eligible patients and invites them to view a less than 10-minute standardized informed decision-making video providing standard information about appendicitis and the different treatment options (offered in English and Spanish versions, <https://www.youtube.com/playlist?list=PLQUQ6jdR0MPag-a8CvSdhVwnuYzNKF9tu>).

Participants who decline randomization are asked to participate in the observational cohort (with similar baseline and follow-up measures as participants in the RCT). All patients are asked for permission to be followed through passive electronic medical record (EMR) review.

Participant Follow Up Assessment:

Participants are contacted 24-48 hours after discharge by a member of the research team to answer any questions about the study and review the survey protocol (see Table 1. Participant Assessment Schedule). Participants are then contacted by phone by site research coordinators one and two weeks after enrollment for study assessments. Data collected through the two week assessment are entered by site research coordinators into a REDCap database, which is managed by the University of Washington (UW) data coordinating center (DCC).²⁴ Starting with the Week 4 Assessment, corresponding to our primary endpoint assessment, participants are contacted by phone, mail, or email by the UW Survey Center to complete the remaining study assessments (at 3, 6, 9, 12, 18 and 24 month surveys).. The UW

Survey Center uses the DatStat survey platform (DatStat, Inc., Seattle, WA) to create individualized outreach plans that optimize survey completion rates. Outreach methods are modified to accommodate a participant's preferred mode of contact (email, mail, phone) as well as time of day for contact (if by phone). If a participant requests to speak with a medical provider or has concerning medical symptoms reported to the research team, the clinical team via the surgical site lead is contacted to call the participant for further follow up.

Table 1. Participant Assessment Schedule.

Item	Baseline	Follow-Up Time Point								
		First 4 Weeks			Month					
		1	2	4	3	6	9	12	18	24
Participant Point of Contact	Site Research Team (RT)	Site RT		Survey Center						
Contact Information	X	X	X	X	X	X	X	X	X	X
EQ-5D ²⁵	X			X	X	X	X	X	X	X
10-PROMIS Global Health Short Form ²⁶	X			X	X			X	X	X
PROMIS-Pain Intensity	X	X	X							
Symptom Onset	X									
Additional Demographics*	X									
Treatment Satisfaction/Expectation	X			X	X**					
Gastrointestinal Quality of Life (GIQLI) ²⁷				X	X			X	X	X
Healthcare Utilization		X	X	X	X	X	X	X	X	X
Signs & Symptoms of Appendicitis		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Decision Regret Scale ²⁸				X	X			X		
Major Life Changes				X	X	X	X	X	X	X
Work Productivity Index		X	X	X	X					
Return to Work Information		X	X	X	X**					
Medication Use		X	X	X	X**					
Treatment Strategy Change		X	X	X						

*Includes the following topics: Demographics & Gender Identity, Caregiver Role, Instrumental Support, Employment/Student Status, Income, Pain Catastrophizing, Health Literacy, Social Support, Confidence in Treatment Success, Trust in Healthcare

**Only asked if the one month results have not normalized

The DCC performs early quality assurance checks by running REDCap data quality reports. These reports identify missing values for required fields, incorrect data type, range checks, outliers, hidden fields that contain values, and multiple choice fields with

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3 invalid values. Values that need to be corrected are brought to the attention of the
4 research staff at that site.
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7 **Study Arms**

8 Antibiotics Therapy Arm

9 Patients in the antibiotics treatment arm receive a minimum of 24 hours of
10 treatment using an intravenous (IV) antibiotic formulation (administered in q8, q12, or
11 q24 hour regimens) followed by oral antibiotics for a total of a 10-day antibiotic course.
12 Patients are offered a treatment regimen of antibiotics based on guidelines published
13 jointly by the Surgical Infection Society (SIS) and the Infectious Disease Society of
14 America (IDSA) for intravenous antibiotics²⁹ and oral antibiotics based on *in vitro* activity
15 against aerobic and anaerobic Gram-negative bacteria, practical experience with oral
16 antibiotic regimens used to treat diverticulitis, and IDSA/SIS guidelines. The first dose of
17 antibiotics is given in the ED at the time of diagnosis of appendicitis and a total
18 outpatient regimen of antibiotics is an option for patients meeting ED discharge criteria.
19 Antibiotics are procured from the pharmacy by the patient as per usual clinical care.
20
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22 Appendectomy is recommended only if there is development of diffuse peritonitis,
23 development of septic shock³⁰, and/or worsening signs and symptoms of appendicitis
24 after 48 hours. The decision to perform an appendectomy in participants randomized to
25 antibiotics is made by the treating surgeon after consultation with the study clinical
26 research lead to confirm that the above criteria have been satisfied.
27

28 Standard discharge criteria are applied to those treated in the ED and those who
29 are admitted, and the criteria include tolerance of liquids, adequate pain control, and
30 improving clinical condition. All participants are contacted at 24-48 hours by the research
31 coordinator to review the study protocol for follow-up assessments.
32

33 Follow-up with the clinical team is per usual care at each institution. Participants
34 in the antibiotics arm who return to any of the study sites during the follow-up period with
35 recurrent appendicitis are not re-randomized but are offered the choice of either
36 appendectomy or another antibiotic course, if treating surgeon agrees their recurrence
37 can be treated with either option.
38

39 Appendectomy Therapy Arm

40 All patients randomized to appendectomy receive preoperative antibiotics per
41 hospital standards for surgical infection prevention protocols. Appendectomy is
42 performed by an open or laparoscopic approach, depending on patient and surgeon
43 preference.
44

45 **Blinding and Randomization**

46 This is an un-blinded study as patients will know if they were randomized to
47 appendectomy or antibiotics. A separate data coordinating center (DCC) at the
48 University of Washington (UW) generates and maintains randomization lists for each
49 practice site. Using block randomization optimizes the chances of equal numbers of
50 subjects being randomized to each treatment arm and that treatment is balanced at
51 periodic enrollment intervals. Randomization is further stratified by the presence of
52 appendicolith. All other subgroups of interest will be sufficiently large such that the risk
53 of a meaningful imbalance in treatment groups by chance is unlikely. A web-based
54 portal provides the randomized treatment assignment.
55

56 **Outcomes and Measures**

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The primary outcome for the CODA trial is the EQ-5D index reported four weeks after randomization. Important clinical outcomes include major complications and resolution of symptoms by four weeks, eventual appendectomy (due to failure in clinical improvement, progression of disease severity or due to recurrent appendicitis), pain, narcotic use, recurrent episodes of appendicitis, ED visits for abdominal pain/repeat imaging, need for more complicated surgical procedure including laparoscopic converted to open appendectomy and ileocecectomy, rates of perforation, and rates of future small bowel obstructions and hernia development through two years. Complications in both treatment groups are tracked and adjudicated by an independent safety monitor to determine their relation to the disease and treatment. Secondary PROs include a measure of decisional regret, anxiety, additional QoL measures (PROMIS-Global, Gastrointestinal Quality of Life Index (GIQLI)), days missed from work or school, time in healthcare, measures of caregiver burden, and out-of-pocket expenses.

Sample Size

The sample size was calculated based on the difference in EQ-5D between the two treatment interventions. EQ-5D. (see Table 2) The EQ-5D QoL index ranges from 0 (worst QoL) to 1 (highest QoL), where anchor-based methods have shown that the minimally clinically important difference ranges 5%-10%.³¹ Based on data from a prior study of appendectomy with EQ-5D scores at 12 weeks,³² we estimate that the average EQ-5D for the participants randomized to appendectomy will be 0.90 with a standard deviation of 0.12. In order to assess QoL differences between interventions, a total of 1,552 patients will be enrolled, assuming a 90% follow-up at 4-weeks. This will give the study very high power (>99%) to rule out an EQ-5D difference between groups as small as 5% (if treatment differences of 0 to 2% are observed) and 80% power if a treatment difference of 3% is observed.²²

Table 2. Statistical power to declare non-inferiority on patient-reported quality of life, overall and by subgroup (Non-inferiority Margin, M = -5%, one-sided alpha=0.025).

Treatment Difference, Δ	Overall	Subgroups		
	N=1552	N=250	N=400	N=500
-3%	82.6%	-	-	-
-2%	99.4%	-	57.1%	67.9%
-1%	100%	62.4%	83.8%	91.4%
0%	100%	83.0%	96.4%	98.8%

Based on pilot data, stakeholder engagement, and we estimate a randomization rate of 30% of all potential patients. Based on current appendectomy volume at the hospitals participating in the trial, recruitment is planned for three years with potential for extension through four years.

Statistical Analysis

We will assess the EQ-5D at four weeks, using a linear regression model that adjusts for an indicator of randomized treatment group assignment and for all factors used to stratify randomization (i.e., recruitment site, presence of appendicolith). As recommended by the US Food and Drug Administration guidelines on clinical trial design, the estimated treatment effect and 97.5% one-sided confidence interval (CI) will be compared to the non-inferiority margin (M = -5%).³³⁻³⁶ We will conclude that

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3 antibiotics are non-inferior to appendectomy if the entire 97.5% one-sided CI is greater
4 than M, as in example scenario A (Figure 1). This is equivalent to a one-sided
5 ($\alpha=0.025$) test of the null hypothesis $H_0: \Delta \leq -5\%$, for which Δ represents the
6 difference in mean EQ-5D at 4-weeks comparing antibiotics-first to appendectomy-first
7 treatment assignment. If the null hypothesis of $H_0: \Delta \leq -5\%$ is rejected at the final
8 evaluation, then we will conduct a test of superiority to determine the level of statistical
9 evidence supporting an alternative hypothesis $H_A: \Delta > 0\%$ (i.e., scenario B of Figure 1).

10
11 Important clinical endpoints (30-day major complications, days until resolution of
12 symptoms, rates of perforated appendicitis, extent of operation and surgical
13 complications, complications associated with antibiotics, hospital days, number of days
14 using antibiotics beyond the initial treatment, clinic visits, and caregiver/patient “time in
15 healthcare”) will also be compared between ITT groups using regression models
16 appropriate to each endpoint (e.g., linear, logistic, Poisson, or Cox proportional hazards
17 regression models), along with a similar non-inferiority framework.

18 19 20 **Secondary Analyses**

21 We aim to include a heterogeneous population of patients and healthcare
22 settings and plan to explore differences in treatment outcomes across subgroups of
23 interest, including those with appendicolith, people with specific imaging findings
24 including possible appendiceal perforation, those in different age groups (18-64 or ≥ 65),
25 sex, and those whose outcomes may vary due to differences in work and insurance
26 status, comorbidities, or social support. We will evaluate difference in treatment
27 effectiveness based on modality of receipt of antibiotics (all outpatient vs
28 inpatient/outpatient). We will separately assess treatment effect heterogeneity by adding
29 to the primary outcome model an interaction term between the categorical subgroup
30 variable of interest and the indicator of treatment. We will use a global likelihood ratio
31 test to examine if the treatment effect differs between key subgroups of interest.

32 An intention-to-treat (ITT) approach will be applied in the primary analysis. We
33 will conduct a secondary as-treated analysis of the primary outcome measure that
34 appropriately accounts for patient- or provider-level characteristics found to be
35 differentially represented among patients who start in the antibiotics arm and who
36 undergo appendectomy before 24 hours of treatment, or patients who are randomized to
37 appendectomy but refuse the procedure and continue on antibiotics. We will consider a
38 two-stage approach for this as-treated analysis: 1) to identify subgroups that are likely to
39 require appendectomy and therefore should not be considered good candidates for
40 treatment with antibiotics as primary treatment strategy, and; 2) to estimate the complier
41 average causal effect (CACE), which seeks to compare the outcomes of patients treated
42 successfully in the antibiotic treatment arm (i.e., did not ultimately have surgery) with
43 patients randomized to the appendectomy arm who are similar in their expected
44 compliance to assigned treatment.³⁷⁻³⁹ We will use a maximum likelihood mixture
45 modeling approach to identify the optimal comparison group from the control arm for
46 observed compliers in the intervention arm. Secondary analyses of the primary outcome
47 measures will include examining the entire trajectory of EQ-5D QoL measurements for
48 each patient using linear mixed effects models for longitudinal data.⁴⁰ Lastly, a
49 composite outcome metric (symptom resolution without complication) was used in the
50 recently completed pilot trial and will be included as an exploratory measure.²² Because
51 the composite outcome includes only clinical domains, and is relevant to both treatment
52 groups, this may be a helpful measure for clinicians considering the two treatments.

53 54 55 **Data Safety and Monitoring**

Event Reporting:

Death, life threatening events and rehospitalization (other than for treatment of appendicitis) are classified as SAEs. Morbidity events (using modified definitions from NSQIP to accommodate non-operative care) are considered AEs. Adverse events (AEs), serious adverse events (SAEs) and appendectomy after starting antibiotic treatment are identified through 3 approaches; EMR review, patient surveys and through ad hoc reporting by any research or care team member. All SAEs are adjudicated by an independent safety monitor. SAEs and AEs are reviewed by the DSMB biannually (with the exception of death which is reported to the DSMB within 24-hours). An independent Data and Safety Monitoring Board (DSMB) reviews the accruing data to: 1) ensure that study conduct, enrollment, and patient follow-up is adequate; 2) ensure that there are no serious safety concerns; and 3) assess evidence related to patient-reported QoL. The analysis of accruing data is completed by the DCC and interim analysis is presented to the DSMB with the primary goal of monitoring safety outcomes by randomization group. Interim monitoring for SAE and AE will focus on the first four weeks of follow-up. The DSMB will conduct interim analyses at 12, 24, and 36 months.

The CODA trial does not include a stopping rule if non-inferiority is met before complete accrual or if it is determined that non-inferiority cannot be demonstrated in interim analyses. We are not employing a stopping rule because there are important secondary outcomes (e.g rate of eventual appendectomy, complications, subgroup analysis) and understudied subgroups that require full enrollment.

DISCUSSION

Prior trials randomizing patients with appendicitis to antibiotics compared to appendectomy focused on disease cure, with the primary outcome being the rate of appendectomy among antibiotic-treated participants. Previous studies of more than 800 participants randomized to antibiotics suggested that the treatment did not increase the rate of complications and offered as high as a 75% chance of avoiding appendectomy within a year.^{6-9 12 41} What remains to be evaluated is the comparative effectiveness of the two candidate treatments based on a comprehensive assessment of impact, including the full range of clinical outcomes and PROs that matter most to patients. CODA's pragmatic design aims to evaluate antibiotics in a heterogeneous population and practice settings in a large randomized trial, with a parallel observational cohort to assess selection bias. One of the greatest novelties of the CODA trial is its patient centeredness, demonstrated both by the engagement of patients and other stakeholders as partners in selecting the topic, designing the proposal, developing the protocol and overseeing operations, as well as in the selection of a QoL endpoint for the primary analysis.

CODA was designed to directly inform patient and clinician decision-making in the community and several pragmatic features were added to make sure it accounted for the diverse aspects of the population, practice settings, and practices in the US. As a pragmatic trial, CODA has limited exclusion criteria and incorporates the many ways clinical care is delivered across sites of practice. The protocol allows patients in either study arm to leave the healthcare setting as soon as standard discharge criteria are met, including the possibility of completely outpatient care. CODA takes place in diverse study sites (academic, private, public, community, and county hospitals) with patients from a wide range of demographic and socioeconomic characteristics, including both Spanish and English speakers. This enhances the generalizability of the findings, but may compromise study fidelity if patients in any one group have differential treatment

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3 preferences or prove more difficult to contact for follow-up. A downside to this approach
4 is that by including nearly all patients with appendicitis (including those with
5 appendicolith and radiographic findings of perforation who may be at higher risk for
6 requiring an appendectomy) and those undergoing total outpatient antibiotics (which
7 clinicians have less experience with) there is a risk of subgroups with very different
8 outcomes from the broader population and a skewing of the average study results. Using
9 Thorpe's PRECIS rubric for pragmatic trials, the proposed study is considered highly
10 pragmatic, intended to improve the generalization and precision of decision-making
11 beyond the prior randomized studies.⁴²
12

13
14 The results from the European trials of antibiotics have not significantly changed
15 care delivery in the US and have been met with resistance, in part due to the evidence
16 gaps cited earlier and concern about the fate of patients with recurrent disease.⁴³
17 American patients may also have different expectations and resources that influence
18 perception of treatment success and satisfaction with treatments. One particular protocol
19 component of the European trials that may make them less applicable to the US
20 experience is that prior studies all required an in-hospital convalescence for a fixed
21 period of time for both treatment arms that is double the length of stay that the average
22 US patient experiences. CODA builds on the successful experience of emergency
23 medicine clinicians to manage patients with potentially serious infections as outpatients
24 using risk-stratification and long-acting parenteral antibiotics (e.g., diverticulitis) and its
25 effectiveness will be tested in different practice settings and populations. This novel
26 treatment alternative offers avoidance of hospital admission and may substantially
27 reduce costs compared to surgical treatment,
28

29 Stakeholder input is a key component of the emerging field of patient-centered
30 outcomes research. However, including several types of stakeholders (patients,
31 physicians, payers, and purchasers) does not always result in consensus. The selection
32 of an appropriate analytic outcome for the trial was an example. While prior studies
33 focused on clinical outcome (e.g., rates of appendectomy and surgical complications),
34 patient advisors recognized that these outcome measures are specific to only one
35 treatment arm (and to people treated with antibiotics who proceed to appendectomy)
36 and that standardized measurements of quality of life would be applicable to both and
37 had yet to be rigorously assessed. The EQ-5D has been used in prior studies of
38 appendectomy, but never in comparisons of these two treatments.³² Using the EQ-5D as
39 a primary outcome measure was highly relevant to many, but not all, patients. There is a
40 possibility that the primary analytic outcome analysis (non-inferiority of the EQ-5D) could
41 be positive, but other outcome domains might not be aligned. For this reason, multiple
42 secondary analyses and exploratory endpoints have been selected a priori. Evidence in
43 the field of decision-making suggests that patients want information on multiple domains,
44 but we recognize that multiple outcome domains may also add confusion to
45 interpretation of results and implementation in future practice.
46

47 As in all trials, patients are not required to stay in the treatment arms they are
48 assigned to (non-adherence or crossover); for example, select patients in the antibiotics
49 arm might not be willing to receive 24 hours of antibiotics and opt for an appendectomy
50 despite not meeting clinical trial protocol recommendations, or patients randomized to
51 appendectomy might refuse surgery. While the main analytic approach is an intention to
52 treat framework, careful as-treated and secondary data analyses may be helpful in
53 accounting for such non-adherence/crossover.⁴⁴ DeTry recommends both an ITT and a
54 careful as-treated analysis to address crossovers in non-inferiority trials where non-
55 adherence or crossover is present.⁴⁵ A simple as-treated analysis is problematic
56 because of potential differences in demographic or clinical characteristics that introduce
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3 bias in as-treated group comparisons. Our analytic approach proposed involves a two-
4 stage as-treated analysis and potentially will yield conclusions that differ from ITT
5 analysis. However, the ITT results will be considered the primary analysis and are
6 robustly valid since they only depend on randomization and do not depend on model
7 assumptions required for observational comparisons.⁴⁵
8

9 CODA began recruitment in the Summer/Fall of 2016 and now involves eight
10 hospitals in Washington and California with two hospitals planned to begin recruitment in
11 2017. It is possible that not all clinical sites will continue to contribute patients throughout
12 the entire recruitment period (projected to be 3-4 years). Sub-studies and ancillary
13 studies are being proposed to focus on biomarkers, economic analysis, longer-term
14 results, and other predictors of outcome.

15 In conclusion, the CODA trial was designed to address critical knowledge gaps
16 related to the treatment of appendicitis with antibiotics compared with appendectomy.
17 CODA's stakeholder-informed design and operations, pragmatic design, and inclusion of
18 an innovative approach to outpatient antibiotics aim to inform choices in care for this
19 common condition, and planned subgroup analyses allow for improved decision-making.
20

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26 Methodology Committee.
27

28 **Author Contributions:**

29 Dr. Davidson had full access to all of the data in the study and takes responsibility for the
30 integrity of the data and the accuracy of the data analysis. All authors approved the final
31 manuscript and are accountable for the followings aspects of the work:
32

33 Study concept and design: GD, DF, DT, LK, DL, EW, BC, SM, PH

34 Acquisition of data: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH,
35 AE,DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM

36 Analysis and interpretation of data: GD, DF, DT, LK, DL, EW, BC, SM, PH, EC

37 Drafting of the manuscript: GD, DF, DT, EW, AK, AE, DL

38 Critical revision of the manuscript for important intellectual content: GD, DF, DT,
39 EW, BC, SM, PH, EC

40 Final approval of the manuscript: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW,
41 BC, SM, PH, AE,DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM

42 Statistical analysis: PH, BC, SM, DF, GD, DT

43 Administrative, technical, or material support: EW, EC, AK, DD, AK, HE, JY, KM,
44 ID, KC, KM, BT, CF, DS, RT, EL, AS, GM

45 Study supervision: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH,
46 AE,DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM
47

48 All authors have read and understood BMJ policy on declaration of interests and declare
49 that have no competing interests. Data will be available per PCORI's Data Access and
50 Data Sharing Policy.
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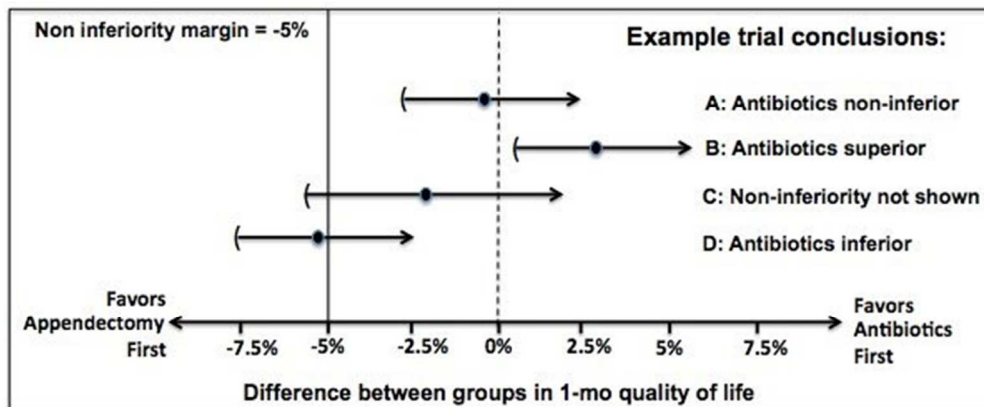


Figure 1

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A Protocol for the Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

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Manuscripts

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A Protocol for the Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

For the CODA Collaborative Investigators:

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Dr. Davidson affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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ABSTRACT

Introduction: Several European studies suggest that some patients with appendicitis can be treated safely with antibiotics. A portion of patients eventually undergo appendectomy within a year, with 10-15% failing to respond in the initial period and a similar additional proportion with suspected recurrent episodes requiring appendectomy. Nearly all patients with appendicitis in the United States (US) are still treated with surgery. A rigorous comparative effectiveness trial in the US that is sufficiently large and pragmatic to incorporate usual variations in care and measures the patient experience is needed to determine if antibiotics are as good as appendectomy.

Objectives: The Comparing Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial for acute appendicitis aims to determine if the antibiotic treatment strategy is non-inferior to appendectomy.

Methods/Analysis: CODA is a randomized, pragmatic non-inferiority trial that aims to recruit 1552 English and Spanish speaking adults with imaging-confirmed appendicitis. Participants are randomized to appendectomy or 10 days of antibiotics (including an option for complete outpatient therapy). A total of 500 patients who decline randomization but consent to follow-up will be included in a parallel observational cohort. The primary analytic outcome is QoL (measured by the EuroQol five dimension [EQ-5D] index) at four weeks. Clinical adverse events, rate of eventual appendectomy, decisional regret, return to work/school, work productivity, and healthcare utilization will be compared. Planned exploratory analyses will identify subpopulations that may have a differential risk of eventual appendectomy in the antibiotic treatment arm.

Ethics and Dissemination: This trial was approved by the University of Washington's Human Subjects Division. Results from this trial will be presented in international conferences and published in peer-review journals.

Trial Registration: Clinicaltrials.org registered on: June 10, 2016 (NCT02800785)

Strengths and Limitations of this Study:

- This trial will evaluate the comparative effectiveness of antibiotics and appendectomy for appendicitis based on a comprehensive assessment of impact, including the full range of clinical outcomes and patient-reported outcomes (PROs) that matter most to patients.
- This pragmatic trial was designed to account for the diverse aspects of the population, practice settings, and practices in the United States.
- This study builds upon the successful experience of emergency medicine clinicians to manage patients with potentially serious infections as outpatients using risk-stratification and long-acting parenteral antibiotics.

INTRODUCTION

Acute appendicitis is the most common reason for an urgent abdominal operation, with a lifetime incidence of 7-15%.¹ Each year nearly 300,000 Americans are hospitalized for appendicitis at a cost of \$7.8 billion.^{2,3} While appendectomy has been

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3 the treatment of choice for 120 years, the successful use of antibiotics was reported both
4 in a series of over 500 patients treated with Streptomycin in the 1950s and later in
5 submariners who did not have access to surgical teams.^{4,5} As anesthesia and surgical
6 safety improved throughout the 20th century, the antibiotics treatment strategy was
7 relegated to patients with disease severe enough (e.g., phlegmon at the cecum,
8 abscess) that surgeons felt there was a higher risk for surgical complications or the need
9 for a more extensive procedure.
10

11 Based on these successes with an antibiotic strategy, in the 1990s European
12 investigators began challenging the notion that surgery was the best approach to treat
13 acute “uncomplicated” appendicitis with a series of randomized trials comparing
14 antibiotics and appendectomy.^{4,6-10} A recent meta-analysis of six randomized trials
15 including 1,724 randomized adult patients concluded there was a high level of efficacy
16 (91% success in the short term with 71% appendectomy free by 1 year), less pain and a
17 quicker return to work in the antibiotic arm.¹¹ The largest, most rigorous and recent trial
18 found a lower rate of post-interventional complications (reported as clinical wound
19 infections, incisional hernia, abdominal pain or obstructive symptoms) in the antibiotics
20 group requiring intervention when compared to those having open surgical procedures.¹²
21 However, in addition to the potential for recurrence of appendicitis, a small proportion of
22 patients treated with antibiotics likely had a neoplasm that would have been incidentally
23 identified had they undergone appendectomy. A recent meta-analysis reported incidental
24 appendiceal neoplasm in 5 of 843 (0.59%) patients undergoing surgery.¹¹ The meta-
25 analysis overall concluded that laparoscopic appendectomy remains the usual treatment
26 for appendicitis and there is a “poor evidence base overall with numerous areas of bias”,
27 limiting the use of the data for decision making.
28

29 The limitations of the existing data regarding antibiotics as a primary treatment
30 for acute appendicitis have been systematically reviewed.¹³ Most studies had small
31 sample sizes; several did not have standardized imaging for diagnosing appendicitis
32 leading to inclusion of patients who likely had “complicated” appendicitis and patients
33 without appendicitis; inexact and subjective outcome definitions and operation/re-
34 operation criteria were utilized; there were limited or no laparoscopic options for surgery,
35 and in some cases, inadequate antibiotic regimens allowed; and most had short follow-
36 up (no studies reported following patients beyond one year).¹³ While some studies
37 evaluated outcomes including general pain scores and use of narcotic pain medication,
38 no study used a validated patient-reported outcome (PRO) tool to measure the patient’s
39 experience in a standardized fashion. Other important outcomes to patients such as
40 impact on work and school productivity, lingering symptoms, decisional regret, and
41 healthcare burden (such as emergency room care or future imaging) were not included
42 in prior studies. Furthermore, prior studies regimented care in ways that are not
43 consistent with care in the United States (US), such as requiring several days of in-
44 hospital convalescence. These limitations may explain the infrequent use of antibiotics
45 as the primary treatment for appendicitis in the US.¹⁴
46

47 In addition to the need to address these limitations, there are additional,
48 unresolved questions that make a larger, more definitive study of this treatment question
49 important. First, there may be important subgroups of people with acute appendicitis
50 who experience the treatment differentially. These might include older patients, who are
51 at higher risk for surgical complications, those with possible appendiceal perforation
52 detected on imaging, or those with an appendicolith. The association between
53 appendicolith and worse outcomes with antibiotics is unclear. Appendicoliths are found
54 in up to 20% of appendicitis cases; a similar proportion is also described in autopsy
55 studies of normal appendices.¹⁵ In several pediatric studies and at least one adult study,
56 appendicolith seemed to be associated with eventual appendectomy; however, since
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3 many trials did not include standardized imaging or criteria for requiring appendectomy
4 following antibiotic therapy for appendicitis, it is unclear if the presence of an
5 appendicolith actually confers a greater risk.^{16 17} There is currently no standard definition
6 of “complicated” disease. In the United States, usual care for appendiceal abscess or
7 pphemon (inflammation so significant that surgeons are concerned for associated
8 surgical morbidity) is antibiotics with consideration for interval appendectomy. Optimal
9 treatment strategies for preoperative radiographic findings of appendiceal perforation is
10 an area of controversy. The use of radiologic imaging to accurately determine
11 perforation is limited; in prior randomized trials, patients with perforation were likely to
12 have been inadvertently included due to a lack of imaging.¹⁸ Finally, the European
13 studies mandated the use of inpatient antibiotics at a time when there was a growing use
14 of outpatient antibiotic regimens for similar conditions, such as acute diverticulitis.¹⁹⁻²¹ A
15 recently completed, pilot randomized trial in the US found that 14 of 15 adults
16 randomized to antibiotics could successfully be discharged from the emergency
17 department (ED) and receive all their care as outpatients, resolving their symptoms of
18 acute appendicitis.²² One of the remaining questions is whether this total outpatient
19 approach to antibiotics would be as good as appendectomy in usual practice.
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21

22 Given these evidence gaps it remains to be determined if, from the patient’s
23 perspective, the antibiotic treatment approach is similar, definitively not worse, and
24 perhaps even superior than the standard treatment of appendectomy. The Comparing
25 Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial was designed to address
26 this question and inform decision-making, focusing on commonly used surgical
27 strategies and a range of antibiotic strategies, including total outpatient therapy, across a
28 broad range of practice environments and a heterogeneous group of patients. These
29 questions provide strong motivation for a pragmatic trial of antibiotics for acute
30 appendicitis.
31
32

33 TRIAL DESIGN

34 Stakeholder Input in Design, Informed Consent, and Protocol

35
36 A central feature of the CODA trial is its engagement of stakeholders in study
37 conception, design, and implementation of the trial.²³ The Stakeholder Coordinating
38 Center (SCC), established as a formal core within the study infrastructure, facilitates all
39 engagement activities. The SCC engages representatives from the patient population of
40 interest (those at risk for or who have had appendicitis), clinicians who are involved in
41 appendicitis treatment (including emergency physicians, nurses, and surgeons), leaders
42 of professional societies (American College of Surgeons and American College of
43 Emergency Physicians), representatives of Accountable Care Organizations, policy-
44 makers, insurers and payers, researchers, and leaders from large, self-insured
45 employers. Specific areas of protocol development informed by the SCC included
46 selecting primary and secondary outcomes. In addition to the routine clinical metrics that
47 are assessed in any study of appendicitis treatment, other outcome measures important
48 to patients (anxiety, quality of life, time away from work, out of pocket expenses) and
49 employers (time away from work and productivity at work) were included. Stakeholder
50 input was particularly helpful in determining the primary analytic outcome, helping weigh
51 the prior evidence showing no difference in rates of complications with an outcome
52 metric that would “sum up” the impact of both treatments on the care experience of
53 patients.
54

55 Because appendectomy was considered the standard and nearly universal
56 therapy in the US, advisors recommended a study that considered the non-inferiority of
57 the antibiotics-first strategy. As one advisor said, “the burden of proof is on the
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3 antibiotics treatment approach to demonstrate that it is as good as appendectomy” (or
4 not inferior by more than a small margin). Advisors also favored a non-inferiority
5 framework because the larger size required for this design would also allow for multiple
6 planned sub-group analyses for patient groups of interest and the possibility that
7 superiority of the PRO measure might be demonstrated. Lastly, advisors suggested a
8 parallel observational cohort to assess for potential selection bias for patients who
9 declined randomization.
10

11 Patient advisors with an experience of incidentally identified neoplasm at the time
12 of appendectomy helped modify the inclusion criteria (excluding all patients with
13 suggestion of mass of the appendix on imaging), consent form (adding language to
14 make sure that patients were informed about this risk, estimated to be 0.6%), and
15 directed a change in the protocol (those with lingering symptoms in the antibiotics group
16 would be directed to follow-up visits and usual care diagnostic evaluations to rule out a
17 neoplasm).
18

19 **Study Aims and Hypothesis**

20 The aims of the study are to compare PROs and clinical outcomes in patients
21 randomized to antibiotics or appendectomy. We hypothesize that antibiotics are non-
22 inferior to appendectomy for PROs and that there are subgroups with better outcomes
23 (clinical and patient-reported) with either treatment. A second set of aims is to perform
24 subpopulation analyses for patients with appendicolith and imaging correlates that may
25 indicate higher risk of requiring appendectomy following initiation of antibiotic therapy,
26 advanced age, sex, comorbid conditions, and insurance status.
27
28

29 **Study population**

30 The study population includes consecutively presenting English or Spanish speaking
31 adults (age ≥ 18 years) with clinically suspected and imaging-confirmed acute
32 appendicitis who present at study site hospital EDs in several states.
33

34 *Exclusion Criteria*

- 35
- 36 • Inability to participate in follow-up (i.e., incarcerated, travel without access to
37 phone, email)
 - 38 • Contraindication to one of the study treatment arms:
 - 39 ○ Septic shock (evidence of severe sepsis or septic shock includes new
40 presumed sepsis-related organ dysfunction, elevated lactate, and/or fluid
41 unresponsive hypotension)
 - 42 ○ Phlegmon for which surgery would not be recommended or diffuse
43 peritonitis for which antibiotics alone would not be recommended
 - 44 ○ Imaging findings of walled off abscess and/or free air
 - 45 ○ Appendiceal soft-tissue mass concerning for malignancy
 - 46 • Other conditions precluding study involvement:
 - 47 ○ Uncompensated liver failure
 - 48 ○ Inflammatory bowel disease requiring active medical treatment (e.g.,
49 Crohn's, ulcerative colitis)
 - 50 ○ Pregnancy or expectation of becoming pregnant in the 30 days following
51 baseline/screening.
 - 52 ○ Surgical implant (e.g., left ventricular assist device, peritoneal dialysis)
 - 53 ○ Malignancy requiring active treatment (e.g., chemotherapy)
 - 54 ○ Immunodeficiency (e.g., AIDS)
 - 55 ○ Another infection currently treated with systemic antibiotics
 - 56 ○ Concurrent illness that would otherwise mandate inpatient hospitalization
 - 57
 - 58
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- Severe allergy or reaction to all proposed antibiotics
- Abdominal or pelvic surgery in the past 30 days

Of note, patients with radiologic diagnosis of appendicolith and/or imaging concerning for appendiceal perforation or phlegmon are included if they do not meet the above exclusion criteria and are otherwise eligible.

Recruitment

All patients presenting to the ED with concern for appendicitis are screened by study coordinators (seven days a week, at least 18 hours per day) based on alerts from clinicians, staff, and screening of ED logs. Patients are identified as potential study candidates based on eligibility criteria collected as part of standard care, including confirmatory diagnostic imaging (CT, US, and/or MRI). A research coordinator and a representative from the clinical team confirm the patient's eligibility for the study. A research team member approaches all eligible patients and invites them to view a less than 10-minute standardized informed decision-making video providing standard information about appendicitis and the different treatment options (offered in English and Spanish versions, <https://www.youtube.com/playlist?list=PLQUQ6jdR0MPag-a8CvSdhVwnuYzNKF9tu>).

Participants who decline randomization are asked to participate in the observational cohort (with similar baseline and follow-up measures as participants in the RCT). All patients are asked for permission to be followed through passive electronic medical record (EMR) review.

Participant Follow Up Assessment:

Participants are contacted 24-48 hours after discharge by a member of the research team to answer any questions about the study and review the survey protocol (see Table 1. Participant Assessment Schedule). Participants are then contacted by phone by site research coordinators one and two weeks after enrollment for study assessments. Data collected through the two week assessment are entered by site research coordinators into a REDCap database, which is managed by the University of Washington (UW) data coordinating center (DCC).²⁴ Starting with the Week 4 Assessment, corresponding to our primary endpoint assessment, participants are contacted by phone, mail, or email by the UW Survey Center to complete the remaining study assessments (at 3, 6, 9, 12, 18 and 24 month surveys).. The UW Survey Center uses the DatStat survey platform (DatStat, Inc., Seattle, WA) to create individualized outreach plans that optimize survey completion rates. Outreach methods are modified to accommodate a participant's preferred mode of contact (email, mail, phone) as well as time of day for contact (if by phone). If a participant requests to speak with a medical provider or has concerning medical symptoms reported to the research team, the clinical team via the surgical site lead is contacted to call the participant for further follow up.

Table 1. Participant Assessment Schedule.

Item	Baseline	Follow-Up Time Point									
		First 4 Weeks			Month						
		1	2	4	3	6	9	12	18	24	
Participant Point of Contact	Site Research	Site RT	Survey Center								

	Team (RT)									
Contact Information	X	X	X	X	X	X	X	X	X	X
EQ-5D ²⁵	X			X	X	X	X	X	X	X
10-PROMIS Global Health Short Form ²⁶	X			X	X			X	X	X
PROMIS-Pain Intensity	X	X	X							
Symptom Onset	X									
Additional Demographics*	X									
Treatment Satisfaction/Expectation	X			X	X**					
Gastrointestinal Quality of Life (GIQLI) ²⁷				X	X			X	X	X
Healthcare Utilization		X	X	X	X	X	X	X	X	X
Signs & Symptoms of Appendicitis		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Decision Regret Scale ²⁸				X	X			X		
Major Life Changes				X	X	X	X	X	X	X
Work Productivity Index		X	X	X	X					
Return to Work Information		X	X	X	X**					
Medication Use		X	X	X	X**					
Treatment Strategy Change		X	X	X						

*Includes the following topics: Demographics & Gender Identity, Caregiver Role, Instrumental Support, Employment/Student Status, Income, Pain Catastrophizing, Health Literacy, Social Support, Confidence in Treatment Success, Trust in Healthcare

**Only asked if the one month results have not normalized

The DCC performs early quality assurance checks by running REDCap data quality reports. These reports identify missing values for required fields, incorrect data type, range checks, outliers, hidden fields that contain values, and multiple choice fields with invalid values. Values that need to be corrected are brought to the attention of the research staff at that site.

Study Arms

Antibiotics Therapy Arm

Patients in the antibiotics treatment arm receive a minimum of 24 hours of treatment using an intravenous (IV) antibiotic formulation (administered in q8, q12, or q24 hour regimens) followed by oral antibiotics for a total of a 10-day antibiotic course. Patients are offered a treatment regimen of antibiotics based on guidelines published jointly by the Surgical Infection Society (SIS) and the Infectious Disease Society of America (IDSA) for intravenous antibiotics²⁹ and oral antibiotics based on *in vitro* activity against aerobic and anaerobic Gram-negative bacteria, practical experience with oral antibiotic regimens used to treat diverticulitis, and IDSA/SIS guidelines. The first dose of antibiotics is given in the ED at the time of diagnosis of appendicitis and a total

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3 outpatient regimen of antibiotics is an option for patients meeting ED discharge criteria.
4 Antibiotics are procured from the pharmacy by the patient as per usual clinical care.
5

6 Appendectomy is recommended only if there is development of diffuse peritonitis,
7 development of septic shock³⁰, and/or worsening signs and symptoms of appendicitis
8 after 48 hours. The decision to perform an appendectomy in participants randomized to
9 antibiotics is made by the treating surgeon after consultation with the study clinical
10 research lead to confirm that the above criteria have been satisfied.

11 Standard discharge criteria are applied to those treated in the ED and those who
12 are admitted, and the criteria include tolerance of liquids, adequate pain control, and
13 improving clinical condition. All participants are contacted at 24-48 hours by the research
14 coordinator to review the study protocol for follow-up assessments.
15

16 Follow-up with the clinical team is per usual care at each institution. Participants
17 in the antibiotics arm who return to any of the study sites during the follow-up period with
18 recurrent appendicitis are not re-randomized but are offered the choice of either
19 appendectomy or another antibiotic course, if treating surgeon agrees their recurrence
20 can be treated with either option.
21

22 Appendectomy Therapy Arm

23 All patients randomized to appendectomy receive preoperative antibiotics per
24 hospital standards for surgical infection prevention protocols. Appendectomy is
25 performed by an open or laparoscopic approach, depending on patient and surgeon
26 preference.
27

28 **Blinding and Randomization**

29 This is an un-blinded study as patients will know if they were randomized to
30 appendectomy or antibiotics. A separate data coordinating center (DCC) at the
31 University of Washington (UW) generates and maintains randomization lists for each
32 practice site. Using block randomization optimizes the chances of equal numbers of
33 subjects being randomized to each treatment arm and that treatment is balanced at
34 periodic enrollment intervals. Randomization is further stratified by the presence of
35 appendicolith. All other subgroups of interest will be sufficiently large such that the risk
36 of a meaningful imbalance in treatment groups by chance is unlikely. A web-based
37 portal provides the randomized treatment assignment.
38
39

40 **Outcomes and Measures**

41 The primary outcome for the CODA trial is the EQ-5D index reported four weeks
42 after randomization. In addition, important clinical outcomes include major complications
43 and resolution of symptoms by four weeks, eventual appendectomy (due to failure in
44 clinical improvement, progression of disease severity or due to recurrent appendicitis),
45 pain, narcotic use, recurrent episodes of appendicitis, ED visits for abdominal pain/repeat
46 imaging, need for more complicated surgical procedure including laparoscopic converted
47 to open appendectomy and ileocectomy, rates of perforation, and rates of future small
48 bowel obstructions and hernia development are collected and will be reported through
49 two years. Complications in both treatment groups are tracked and adjudicated by an
50 independent safety monitor to determine their relation to the disease and treatment.
51 Secondary PROs include a measure of decisional regret, anxiety, additional QoL measures
52 (PROMIS-Global, Gastrointestinal Quality of Life Index (GIQLI)), days missed from work
53 or school, time in healthcare, measures of caregiver burden, and out-of-pocket
54 expenses.
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Sample Size

The sample size was calculated based on the difference in EQ-5D between the two treatment interventions. EQ-5D. (see Table 2) The EQ-5D QoL index ranges from 0 (worst QoL) to 1 (highest QoL), where anchor-based methods have shown that the minimally clinically important difference ranges 5%-10%.³¹ Based on data from a prior study of appendectomy with EQ-5D scores at 12 weeks,³² we estimate that the average EQ-5D for the participants randomized to appendectomy will be 0.90 with a standard deviation of 0.12. In order to assess QoL differences between interventions, a total of 1,552 patients will be enrolled, assuming a 90% follow-up at 4-weeks. This will give the study very high power (>99%) to rule out an EQ-5D difference between groups as small as 5% (if treatment differences of 0 to 2% are observed) and 80% power if a treatment difference of 3% is observed.²²

Table 2. Statistical power to declare non-inferiority on patient-reported quality of life, overall and by subgroup (Non-inferiority Margin, M = -5%, one-sided alpha=0.025).

Treatment Difference, Δ	Overall	Subgroups		
	N=1552	N=250	N=400	N=500
-3%	82.6%	-	-	-
-2%	99.4%	-	57.1%	67.9%
-1%	100%	62.4%	83.8%	91.4%
0%	100%	83.0%	96.4%	98.8%

Based on pilot data, stakeholder engagement, and we estimate a randomization rate of 30% of all potential patients. Based on current appendectomy volume at the hospitals participating in the trial, recruitment is planned for three years with potential for extension through four years.

Statistical Analysis

We will assess the EQ-5D at four weeks, using a linear regression model that adjusts for an indicator of randomized treatment group assignment and for all factors used to stratify randomization (i.e., recruitment site, presence of appendicolith). As recommended by the US Food and Drug Administration guidelines on clinical trial design, the estimated treatment effect and 97.5% one-sided confidence interval (CI) will be compared to the non-inferiority margin (M = -5%).³³⁻³⁶ We will conclude that antibiotics are non-inferior to appendectomy if the entire 97.5% one-sided CI is greater than M, as in example scenario A (Figure 1). This is equivalent to a one-sided (alpha=0.025) test of the null hypothesis $H_0: \Delta \leq -5\%$, for which Δ represents the difference in mean EQ-5D at 4-weeks comparing antibiotics-first to appendectomy-first treatment assignment. If the null hypothesis of $H_0: \Delta \leq -5\%$ is rejected at the final evaluation, then we will conduct a test of superiority to determine the level of statistical evidence supporting an alternative hypothesis $H_A: \Delta > 0\%$ (i.e., scenario B of Figure 1).

Important clinical endpoints (30-day major complications, days until resolution of symptoms, rates of perforated appendicitis, extent of operation and surgical complications, complications associated with antibiotics, hospital days, number of days using antibiotics beyond the initial treatment, clinic visits, and caregiver/patient "time in healthcare") will also be compared between ITT groups using regression models appropriate to each endpoint (e.g., linear, logistic, Poisson, or Cox proportional hazards regression models), along with a similar non-inferiority framework.

Secondary Analyses

We aim to include a heterogeneous population of patients and healthcare settings and plan to explore differences in treatment outcomes across subgroups of interest, including those with appendicolith, people with specific imaging findings including possible appendiceal perforation, those in different age groups (18-64 or ≥ 65), sex, and those whose outcomes may vary due to differences in work and insurance status, comorbidities, or social support. We will evaluate difference in treatment effectiveness based on modality of receipt of antibiotics (all outpatient vs inpatient/outpatient). We will separately assess treatment effect heterogeneity by adding to the primary outcome model an interaction term between the categorical subgroup variable of interest and the indicator of treatment. We will use a global likelihood ratio test to examine if the treatment effect differs between key subgroups of interest.

An intention-to-treat (ITT) approach will be applied in the primary analysis. We will conduct a secondary as-treated analysis of the primary outcome measure that appropriately accounts for patient- or provider-level characteristics found to be differentially represented among patients who start in the antibiotics arm and who undergo appendectomy before 24 hours of treatment, or patients who are randomized to appendectomy but refuse the procedure and continue on antibiotics. We will consider a two-stage approach for this as-treated analysis: 1) to identify subgroups that are likely to require appendectomy and therefore should not be considered good candidates for treatment with antibiotics as primary treatment strategy, and; 2) to estimate the complier average causal effect (CACE), which seeks to compare the outcomes of patients treated successfully in the antibiotic treatment arm (i.e., did not ultimately have surgery) with patients randomized to the appendectomy arm who are similar in their expected compliance to assigned treatment.³⁷⁻³⁹ We will use a maximum likelihood mixture modeling approach to identify the optimal comparison group from the control arm for observed compliers in the intervention arm. Secondary analyses of the primary outcome measures will include examining the entire trajectory of EQ-5D QoL measurements for each patient using linear mixed effects models for longitudinal data.⁴⁰ Lastly, a composite outcome metric (symptom resolution without complication) was used in the recently completed pilot trial and will be included as an exploratory measure.²² Because the composite outcome includes only clinical domains, and is relevant to both treatment groups, this may be a helpful measure for clinicians considering the two treatments.

Data Safety and Monitoring

Event Reporting:

Death, life threatening events and rehospitalization (other than for treatment of appendicitis) are classified as SAEs. Morbidity events (using modified definitions from NSQIP to accommodate non-operative care) are considered AEs. Adverse events (AEs), serious adverse events (SAEs) and appendectomy after starting antibiotic treatment are identified through 3 approaches; EMR review, patient surveys and through ad hoc reporting by any research or care team member. All SAEs are adjudicated by an independent safety monitor. SAEs and AEs are reviewed by the DSMB biannually (with the exception of death which is reported to the DSMB within 24-hours). An independent Data and Safety Monitoring Board (DSMB) reviews the accruing data to: 1) ensure that study conduct, enrollment, and patient follow-up is adequate; 2) ensure that there are no serious safety concerns; and 3) assess evidence related to patient-reported QoL. The analysis of accruing data is completed by the DCC and interim analysis is presented to the DSMB with the primary goal of monitoring safety outcomes by randomization group. Interim monitoring for SAE and AE will focus on the

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2
3 first four weeks of follow-up. The DSMB will conduct interim analyses at 12, 24, and 36
4 months.

5
6 The CODA trial does not include a stopping rule if non-inferiority is met before
7 complete accrual or if it is determined that non-inferiority cannot be demonstrated in
8 interim analyses. We are not employing a stopping rule because there are important
9 secondary outcomes (e.g rate of eventual appendectomy, complications, subgroup
10 analysis) and understudied subgroups that require full enrollment.

11 12 **DISCUSSION**

13 Prior trials randomizing patients with appendicitis to antibiotics compared to
14 appendectomy focused on disease cure, with the primary outcome being the rate of
15 appendectomy among antibiotic-treated participants. Previous studies of more than 800
16 participants randomized to antibiotics suggested that the treatment did not increase the
17 rate of complications and offered as high as a 75% chance of avoiding appendectomy
18 within a year.^{6-9 12 41} What remains to be evaluated is the comparative effectiveness of
19 the two candidate treatments based on a comprehensive assessment of impact,
20 including the full range of clinical outcomes and PROs that matter most to patients.
21 CODA's pragmatic design aims to evaluate antibiotics in a heterogeneous population
22 and practice settings in a large randomized trial, with a parallel observational cohort to
23 assess selection bias. One of the greatest novelties of the CODA trial is its patient
24 centeredness, demonstrated both by the engagement of patients and other stakeholders
25 as partners in selecting the topic, designing the proposal, developing the protocol and
26 overseeing operations, as well as in the selection of a QoL endpoint for the primary
27 analysis.
28

29
30 CODA was designed to directly inform patient and clinician decision-making in
31 the community and several pragmatic features were added to make sure it accounted for
32 the diverse aspects of the population, practice settings, and practices in the US. As a
33 pragmatic trial, CODA has limited exclusion criteria and incorporates the many ways
34 clinical care is delivered across sites of practice. The protocol allows patients in either
35 study arm to leave the healthcare setting as soon as standard discharge criteria are met,
36 including the possibility of completely outpatient care. CODA takes place in diverse
37 study sites (academic, private, public, community, and county hospitals) with patients
38 from a wide range of demographic and socioeconomic characteristics, including both
39 Spanish and English speakers. This enhances the generalizability of the findings, but
40 may compromise study fidelity if patients in any one group have differential treatment
41 preferences or prove more difficult to contact for follow-up. A downside to this approach
42 is that by including nearly all patients with appendicitis (including those with
43 appendicolith and radiographic findings of perforation who may be at higher risk for
44 requiring an appendectomy) and those undergoing total outpatient antibiotics (which
45 clinicians have less experience with) there is a risk of subgroups with very different
46 outcomes from the broader population and a skewing of the average study results. Using
47 Thorpe's PRECIS rubric for pragmatic trials, the proposed study is considered highly
48 pragmatic, intended to improve the generalization and precision of decision-making
49 beyond the prior randomized studies.⁴²
50
51

52 The results from the European trials of antibiotics have not significantly changed
53 care delivery in the US and have been met with resistance, in part due to the evidence
54 gaps cited earlier and concern about the fate of patients with recurrent disease.⁴³
55 American patients may also have different expectations and resources that influence
56 perception of treatment success and satisfaction with treatments. One particular protocol
57 component of the European trials that may make them less applicable to the US
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experience is that prior studies all required an in-hospital convalescence for a fixed period of time for both treatment arms that is double the length of stay that the average US patient experiences. CODA builds on the successful experience of emergency medicine clinicians to manage patients with potentially serious infections as outpatients using risk-stratification and long-acting parenteral antibiotics (e.g., diverticulitis) and its effectiveness will be tested in different practice settings and populations. This novel treatment alternative offers avoidance of hospital admission and may substantially reduce costs compared to surgical treatment,

Stakeholder input is a key component of the emerging field of patient-centered outcomes research. However, including several types of stakeholders (patients, physicians, payers, and purchasers) does not always result in consensus. The selection of an appropriate analytic outcome for the trial was an example. While prior studies focused on clinical outcome (e.g., rates of appendectomy and surgical complications), patient advisors recognized that these outcome measures are specific to only one treatment arm (and to people treated with antibiotics who proceed to appendectomy) and that standardized measurements of quality of life would be applicable to both and had yet to be rigorously assessed. The EQ-5D has been used in prior studies of appendectomy, but never in comparisons of these two treatments.³² Using the EQ-5D as a primary outcome measure was highly relevant to many, but not all, patients. There is a possibility that the primary analytic outcome analysis (non-inferiority of the EQ-5D) could be positive, but other outcome domains might not be aligned. For this reason, multiple secondary analyses and exploratory endpoints have been selected a priori. Evidence in the field of decision-making suggests that patients want information on multiple domains, but we recognize that multiple outcome domains may also add confusion to interpretation of results and implementation in future practice.

As in all trials, patients are not required to stay in the treatment arms they are assigned to (non-adherence or crossover); for example, select patients in the antibiotics arm might not be willing to receive 24 hours of antibiotics and opt for an appendectomy despite not meeting clinical trial protocol recommendations, or patients randomized to appendectomy might refuse surgery. While the main analytic approach is an intention to treat framework, careful as-treated and secondary data analyses may be helpful in accounting for such non-adherence/crossover.⁴⁴ Detry recommends both an ITT and a careful as-treated analysis to address crossovers in non-inferiority trials where non-adherence or crossover is present.⁴⁵ A simple as-treated analysis is problematic because of potential differences in demographic or clinical characteristics that introduce bias in as-treated group comparisons. Our analytic approach proposed involves a two-stage as-treated analysis and potentially will yield conclusions that differ from ITT analysis. However, the ITT results will be considered the primary analysis and are robustly valid since they only depend on randomization and do not depend on model assumptions required for observational comparisons.⁴⁵

CODA began recruitment in the Summer/Fall of 2016 and now involves eight hospitals in Washington and California with two hospitals planned to begin recruitment in 2017. It is possible that not all clinical sites will continue to contribute patients throughout the entire recruitment period (projected to be 3-4 years). Sub-studies and ancillary studies are being proposed to focus on biomarkers, economic analysis, longer-term results, and other predictors of outcome.

In conclusion, the CODA trial was designed to address critical knowledge gaps related to the treatment of appendicitis with antibiotics compared with appendectomy. CODA's stakeholder-informed design and operations, pragmatic design, and inclusion of an innovative approach to outpatient antibiotics aim to inform choices in care for this common condition, and planned subgroup analyses allow for improved decision-making.

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Author Contributions: Dr. Davidson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final manuscript and are accountable for the followings aspects of the work:

Study concept and design: GD, DF, DT, LK, DL, EW, BC, SM, PH
 Acquisition of data: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH, AE, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM
 Analysis and interpretation of data: GD, DF, DT, LK, DL, EW, BC, SM, PH, EC
 Drafting of the manuscript: GD, DF, DT, EW, AK, AE, DL
 Critical revision of the manuscript for important intellectual content: GD, DF, DT, EW, BC, SM, PH, EC
 Final approval of the manuscript: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH, AE, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM
 Statistical analysis: PH, BC, SM, DF, GD, DT
 Administrative, technical, or material support: EW, EC, AK, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM
 Study supervision: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH, AE, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM

All authors have read and understood BMJ policy on declaration of interests and declare that have no competing interests. Data will be available per PCORI's Data Access and Data Sharing Policy.

Ethics and Dissemination: This trial was approved by the University of Washington's Human Subjects Division on April 21, 2016 (Version 3.5). The University of Washington serves as the IRB of record for the following study sites: University of Washington Medical Center, Harborview Medical Center, Virginia Mason Medical Center, and Madigan Army Medical Center. Western IRB is the overseeing IRB for Swedish-First Hill (approved July 8, 2016) and Providence Regional Medical Center (approved July 1, 2016). UCLA-Olive View (approved June 12, 2016) and UCLA-Harbor (approved March 4, 2016) are both regulated by their respective institutional IRBs.

Trial Registration: Clinicaltrials.org registered on: June 10, 2016 (NCT02800785)

Figure Legends:

Figure 1. Example study conclusions in the CODA trial. There are four possible study conclusions. A: The observed treatment effect (black circle) of antibiotics is almost zero and the 97.5% one-sided confidence interval (CI, arrow) does not overlap the non-inferiority margin of -5%, indicating antibiotics is a non-interior strategy. B: The observed treatment effect of antibiotics is more than 2.5% better than appendectomy and the CI does not include 0, indicating that antibiotics are superior. C: The observed treatment effect of antibiotics is 2.5% worse than appendectomy but the CI includes -5%, so non-inferiority cannot be claims. D: The observed treatment effect of antibiotics is more than 5% worse than appendectomy, indicating that antibiotics are inferior.

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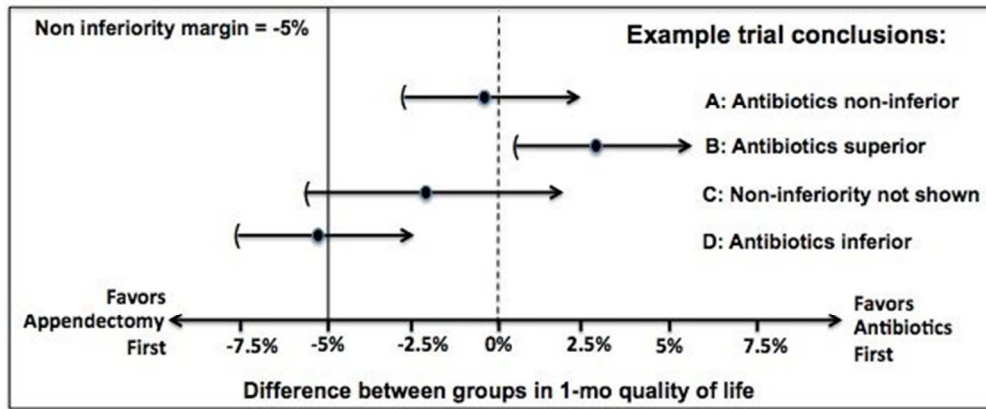


Figure 1

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____
	5b	Name and contact information for the trial sponsor	_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____

1 **Introduction**

2

3 Background and rationale

4 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention _____

5

6 6b Explanation for choice of comparators _____

7

8 Objectives

9 7 Specific objectives or hypotheses _____

10

11 Trial design

12 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____

13

14

15 **Methods: Participants, interventions, and outcomes**

16

17 Study setting

18 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained _____

19

20 Eligibility criteria

21 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) _____

22

23 Interventions

24 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered _____

25

26 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) _____

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) _____

29

30 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____

31

32

33 Outcomes

34 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended _____

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41 Participant timeline

42 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) _____

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____
 2 clinical and statistical assumptions supporting any sample size calculations

3
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____
 5

6
 7 **Methods: Assignment of interventions (for controlled trials)**
 8

9 Allocation:

10
 11 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____
 12 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 13 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 14 or assign interventions

15
 16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism

19
 20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____
 21 interventions

22
 23 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____
 24 assessors, data analysts), and how

25
 26 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____
 27 allocated intervention during the trial

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 32 **Methods: Data collection, management, and analysis**
 33

34 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____
 35 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 37 Reference to where data collection forms can be found, if not in the protocol

38
 39
 40 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____
 41 collected for participants who discontinue or deviate from intervention protocols

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	_____
2			(eg, double data entry; range checks for data values). Reference to where details of data management	
3			procedures can be found, if not in the protocol	
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	_____
6			statistical analysis plan can be found, if not in the protocol	
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	_____
11			statistical methods to handle missing data (eg, multiple imputation)	
12				
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15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	_____
18			whether it is independent from the sponsor and competing interests; and reference to where further details	
19			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	
20			needed	
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	_____
23			results and make the final decision to terminate the trial	
24				
25				
26	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	_____
27			events and other unintended effects of trial interventions or trial conduct	
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	_____
30			from investigators and the sponsor	
31				
32				
33	Ethics and dissemination			
34				
35	Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____
36	approval			
37				
38	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	_____
39	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
40			regulators)	
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and	_____
2			how (see Item 32)	
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	_____
5			studies, if applicable	
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained	_____
8			in order to protect confidentiality before, during, and after the trial	
9				
10	Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____
11	interests			
12				
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that	_____
15			limit such access for investigators	
16				
17	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	_____
18	trial care		participation	
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals,	_____
21			the public, and other relevant groups (eg, via publication, reporting in results databases, or other data	
22			sharing arrangements), including any publication restrictions	
23				
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
28				
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30	Appendices			
31				
32	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
33	materials			
34				
35	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	_____
36	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
37				

38
39 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
40 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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BMJ Open

A Protocol for the Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

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Secondary Subject Heading:	Research methods, Patient-centred medicine, Evidence based practice, Emergency medicine

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Keywords:	Adult surgery < SURGERY, Patient-centered research, Appendicitis, Treatment options

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A Protocol for the Pragmatic Randomized Study of Appendicitis Treatment: The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial

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Dr. Davidson affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Word Count: 5366

ABSTRACT

Introduction: Several European studies suggest that some patients with appendicitis can be treated safely with antibiotics. A portion of patients eventually undergo appendectomy within a year, with 10-15% failing to respond in the initial period and a similar additional proportion with suspected recurrent episodes requiring appendectomy. Nearly all patients with appendicitis in the United States (US) are still treated with surgery. A rigorous comparative effectiveness trial in the US that is sufficiently large and pragmatic to incorporate usual variations in care and measures the patient experience is needed to determine if antibiotics are as good as appendectomy.

Objectives: The Comparing Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial for acute appendicitis aims to determine if the antibiotic treatment strategy is non-inferior to appendectomy.

Methods/Analysis: CODA is a randomized, pragmatic non-inferiority trial that aims to recruit 1552 English and Spanish speaking adults with imaging-confirmed appendicitis. Participants are randomized to appendectomy or 10 days of antibiotics (including an option for complete outpatient therapy). A total of 500 patients who decline randomization but consent to follow-up will be included in a parallel observational cohort. The primary analytic outcome is QoL (measured by the EuroQol five dimension [EQ-5D] index) at four weeks. Clinical adverse events, rate of eventual appendectomy, decisional regret, return to work/school, work productivity, and healthcare utilization will be compared. Planned exploratory analyses will identify subpopulations that may have a differential risk of eventual appendectomy in the antibiotic treatment arm.

Ethics and Dissemination: This trial was approved by the University of Washington's Human Subjects Division. Results from this trial will be presented in international conferences and published in peer-review journals.

Trial Registration: Clinicaltrials.org registered on: June 10, 2016 (NCT02800785)

Strengths and Limitations of this Study:

- This trial will evaluate the comparative effectiveness of antibiotics and appendectomy for appendicitis based on a comprehensive assessment of impact, including the full range of clinical outcomes and patient-reported outcomes (PROs) that matter most to patients.
- This pragmatic trial was designed to account for the diverse aspects of the population, practice settings, and practices in the United States.
- This study builds upon the successful experience of emergency medicine clinicians to manage patients with potentially serious infections as outpatients using risk-stratification and long-acting parenteral antibiotics.

INTRODUCTION

Acute appendicitis is the most common reason for an urgent abdominal operation, with a lifetime incidence of 7-15%.¹ Each year nearly 300,000 Americans are hospitalized for appendicitis at a cost of \$7.8 billion.^{2,3} While appendectomy has been

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3 the treatment of choice for 120 years, the successful use of antibiotics was reported both
4 in a series of over 500 patients treated with Streptomycin in the 1950s and later in
5 submariners who did not have access to surgical teams.^{4,5} As anesthesia and surgical
6 safety improved throughout the 20th century, the antibiotics treatment strategy was
7 relegated to patients with disease severe enough (e.g., phlegmon at the cecum,
8 abscess) that surgeons felt there was a higher risk for surgical complications or the need
9 for a more extensive procedure.
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11 Based on these successes with an antibiotic strategy, in the 1990s European
12 investigators began challenging the notion that surgery was the best approach to treat
13 acute “uncomplicated” appendicitis with a series of randomized trials comparing
14 antibiotics and appendectomy.^{4,6-10} A recent meta-analysis of six randomized trials
15 including 1,724 randomized adult patients concluded there was a high level of efficacy
16 (91% success in the short term with 71% appendectomy free by 1 year), less pain and a
17 quicker return to work in the antibiotic arm.¹¹ The largest, most rigorous and recent trial
18 found a lower rate of post-interventional complications (reported as clinical wound
19 infections, incisional hernia, abdominal pain or obstructive symptoms) in the antibiotics
20 group requiring intervention when compared to those having open surgical procedures.¹²
21 However, in addition to the potential for recurrence of appendicitis, a small proportion of
22 patients treated with antibiotics likely had a neoplasm that would have been incidentally
23 identified had they undergone appendectomy. A recent meta-analysis reported incidental
24 appendiceal neoplasm in 5 of 843 (0.59%) patients undergoing surgery.¹¹ The meta-
25 analysis overall concluded that laparoscopic appendectomy remains the usual treatment
26 for appendicitis and there is a “poor evidence base overall with numerous areas of bias”,
27 limiting the use of the data for decision making.
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29 The limitations of the existing data regarding antibiotics as a primary treatment
30 for acute appendicitis have been systematically reviewed.¹³ Most studies had small
31 sample sizes; several did not have standardized imaging for diagnosing appendicitis
32 leading to inclusion of patients who likely had “complicated” appendicitis and patients
33 without appendicitis; inexact and subjective outcome definitions and operation/re-
34 operation criteria were utilized; there were limited or no laparoscopic options for surgery,
35 and in some cases, inadequate antibiotic regimens allowed; and most had short follow-
36 up (no studies reported following patients beyond one year).¹³ While some studies
37 evaluated outcomes including general pain scores and use of narcotic pain medication,
38 no study used a validated patient-reported outcome (PRO) tool to measure the patient’s
39 experience in a standardized fashion. Other important outcomes to patients such as
40 impact on work and school productivity, lingering symptoms, decisional regret, and
41 healthcare burden (such as emergency room care or future imaging) were not included
42 in prior studies. Furthermore, prior studies regimented care in ways that are not
43 consistent with care in the United States (US), such as requiring several days of in-
44 hospital convalescence. These limitations may explain the infrequent use of antibiotics
45 as the primary treatment for appendicitis in the US.¹⁴
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48 In addition to the need to address these limitations, there are additional,
49 unresolved questions that make a larger, more definitive study of this treatment question
50 important. First, there may be important subgroups of people with acute appendicitis
51 who experience the treatment differentially. These might include older patients, who are
52 at higher risk for surgical complications, those with possible appendiceal perforation
53 detected on imaging, or those with an appendicolith. The association between
54 appendicolith and worse outcomes with antibiotics is unclear. Appendicoliths are found
55 in up to 20% of appendicitis cases; a similar proportion is also described in autopsy
56 studies of normal appendices.¹⁵ In several pediatric studies and at least one adult study,
57 appendicolith seemed to be associated with eventual appendectomy; however, since
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3 many trials did not include standardized imaging or criteria for requiring appendectomy
4 following antibiotic therapy for appendicitis, it is unclear if the presence of an
5 appendicolith actually confers a greater risk.^{16 17} There is currently no standard definition
6 of “complicated” disease. In the United States, usual care for appendiceal abscess or
7 pphemon (inflammation so significant that surgeons are concerned for associated
8 surgical morbidity) is antibiotics with consideration for interval appendectomy. Optimal
9 treatment strategies for preoperative radiographic findings of appendiceal perforation is
10 an area of controversy. The use of radiologic imaging to accurately determine
11 perforation is limited; in prior randomized trials, patients with perforation were likely to
12 have been inadvertently included due to a lack of imaging.¹⁸ Finally, the European
13 studies mandated the use of inpatient antibiotics at a time when there was a growing use
14 of outpatient antibiotic regimens for similar conditions, such as acute diverticulitis.¹⁹⁻²¹ A
15 recently completed, pilot randomized trial in the US found that 14 of 15 adults
16 randomized to antibiotics could successfully be discharged from the emergency
17 department (ED) and receive all their care as outpatients, resolving their symptoms of
18 acute appendicitis.²² One of the remaining questions is whether this total outpatient
19 approach to antibiotics would be as good as appendectomy in usual practice.
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22 Given these evidence gaps it remains to be determined if, from the patient’s
23 perspective, the antibiotic treatment approach is similar, definitively not worse, and
24 perhaps even superior than the standard treatment of appendectomy. The Comparing
25 Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial was designed to address
26 this question and inform decision-making, focusing on commonly used surgical
27 strategies and a range of antibiotic strategies, including total outpatient therapy, across a
28 broad range of practice environments and a heterogeneous group of patients. These
29 questions provide strong motivation for a pragmatic trial of antibiotics for acute
30 appendicitis.
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33 TRIAL DESIGN

34 Stakeholder Input in Design, Informed Consent, and Protocol

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36 A central feature of the CODA trial is its engagement of stakeholders in study
37 conception, design, and implementation of the trial.²³ The Stakeholder Coordinating
38 Center (SCC), established as a formal core within the study infrastructure, facilitates all
39 engagement activities. The SCC engages representatives from the patient population of
40 interest (those at risk for or who have had appendicitis), clinicians who are involved in
41 appendicitis treatment (including emergency physicians, nurses, and surgeons), leaders
42 of professional societies (American College of Surgeons and American College of
43 Emergency Physicians), representatives of Accountable Care Organizations, policy-
44 makers, insurers and payers, researchers, and leaders from large, self-insured
45 employers. Specific areas of protocol development informed by the SCC included
46 selecting primary and secondary outcomes. In addition to the routine clinical metrics that
47 are assessed in any study of appendicitis treatment, other outcome measures important
48 to patients (anxiety, quality of life, time away from work, out of pocket expenses) and
49 employers (time away from work and productivity at work) were included. Stakeholder
50 input was particularly helpful in determining the primary analytic outcome, helping weigh
51 the prior evidence showing no difference in rates of complications with an outcome
52 metric that would “sum up” the impact of both treatments on the care experience of
53 patients.
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55 Because appendectomy was considered the standard and nearly universal
56 therapy in the US, advisors recommended a study that considered the non-inferiority of
57 the antibiotics-first strategy. As one advisor said, “the burden of proof is on the
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3 antibiotics treatment approach to demonstrate that it is as good as appendectomy” (or
4 not inferior by more than a small margin). Advisors also favored a non-inferiority
5 framework because the larger size required for this design would also allow for multiple
6 planned sub-group analyses for patient groups of interest and the possibility that
7 superiority of the PRO measure might be demonstrated. Lastly, advisors suggested a
8 parallel observational cohort to assess for potential selection bias for patients who
9 declined randomization.
10

11 Patient advisors with an experience of incidentally identified neoplasm at the time
12 of appendectomy helped modify the inclusion criteria (excluding all patients with
13 suggestion of mass of the appendix on imaging), consent form (adding language to
14 make sure that patients were informed about this risk, estimated to be 0.6%), and
15 directed a change in the protocol (those with lingering symptoms in the antibiotics group
16 would be directed to follow-up visits and usual care diagnostic evaluations to rule out a
17 neoplasm).
18

19 **Study Aims and Hypothesis**

20 The aims of the study are to compare PROs and clinical outcomes in patients
21 randomized to antibiotics or appendectomy. We hypothesize that antibiotics are non-
22 inferior to appendectomy for PROs and that there are subgroups with better outcomes
23 (clinical and patient-reported) with either treatment. A second set of aims is to perform
24 subpopulation analyses for patients with appendicolith and imaging correlates that may
25 indicate higher risk of requiring appendectomy following initiation of antibiotic therapy,
26 advanced age, sex, comorbid conditions, and insurance status.
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29 **Study population**

30 The study population includes consecutively presenting English or Spanish speaking
31 adults (age ≥ 18 years) with clinically suspected and imaging-confirmed acute
32 appendicitis who present at study site hospital EDs in several states.
33

34 *Exclusion Criteria*

- 35
- 36 • Inability to participate in follow-up (i.e., incarcerated, travel without access to
37 phone, email)
 - 38 • Contraindication to one of the study treatment arms:
 - 39 ○ Septic shock (evidence of severe sepsis or septic shock includes new
40 presumed sepsis-related organ dysfunction, elevated lactate, and/or fluid
41 unresponsive hypotension)
 - 42 ○ Phlegmon for which surgery would not be recommended or diffuse
43 peritonitis for which antibiotics alone would not be recommended
 - 44 ○ Imaging findings of walled off abscess and/or free air
 - 45 ○ Appendiceal soft-tissue mass concerning for malignancy
 - 46 • Other conditions precluding study involvement:
 - 47 ○ Uncompensated liver failure
 - 48 ○ Inflammatory bowel disease requiring active medical treatment (e.g.,
49 Crohn's, ulcerative colitis)
 - 50 ○ Pregnancy or expectation of becoming pregnant in the 30 days following
51 baseline/screening.
 - 52 ○ Surgical implant (e.g., left ventricular assist device, peritoneal dialysis)
 - 53 ○ Malignancy requiring active treatment (e.g., chemotherapy)
 - 54 ○ Immunodeficiency (e.g., AIDS)
 - 55 ○ Another infection currently treated with systemic antibiotics
 - 56 ○ Concurrent illness that would otherwise mandate inpatient hospitalization
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- Severe allergy or reaction to all proposed antibiotics
- Abdominal or pelvic surgery in the past 30 days

Of note, patients with radiologic diagnosis of appendicolith and/or imaging concerning for appendiceal perforation or phlegmon are included if they do not meet the above exclusion criteria and are otherwise eligible.

Recruitment

All patients presenting to the ED with concern for appendicitis are screened by study coordinators (seven days a week, at least 18 hours per day) based on alerts from clinicians, staff, and screening of ED logs. Patients are identified as potential study candidates based on eligibility criteria collected as part of standard care, including confirmatory diagnostic imaging (CT, US, and/or MRI). A research coordinator and a representative from the clinical team confirm the patient's eligibility for the study. A research team member approaches all eligible patients and invites them to view a less than 10-minute standardized informed decision-making video providing standard information about appendicitis and the different treatment options (offered in English and Spanish versions, <https://www.youtube.com/playlist?list=PLQUQ6jdR0MPag-a8CvSdhVwnuYzNKF9tu>).

Participants who decline randomization are asked to participate in the observational cohort (with similar baseline and follow-up measures as participants in the RCT). All patients are asked for permission to be followed through passive electronic medical record (EMR) review.

Participant Follow Up Assessment:

Participants are contacted 24-48 hours after discharge by a member of the research team to answer any questions about the study and review the survey protocol (see Table 1. Participant Assessment Schedule). Participants are then contacted by phone by site research coordinators one and two weeks after enrollment for study assessments. Data collected through the two week assessment are entered by site research coordinators into a REDCap database, which is managed by the University of Washington (UW) data coordinating center (DCC).²⁴ Starting with the Week 4 Assessment, corresponding to our primary endpoint assessment, participants are contacted by phone, mail, or email by the UW Survey Center to complete the remaining study assessments (at 3, 6, 9, 12, 18 and 24 month surveys).. The UW Survey Center uses the DatStat survey platform (DatStat, Inc., Seattle, WA) to create individualized outreach plans that optimize survey completion rates. Outreach methods are modified to accommodate a participant's preferred mode of contact (email, mail, phone) as well as time of day for contact (if by phone). If a participant requests to speak with a medical provider or has concerning medical symptoms reported to the research team, the clinical team via the surgical site lead is contacted to call the participant for further follow up.

Table 1. Participant Assessment Schedule.

Item	Baseline	Follow-Up Time Point									
		First 4 Weeks			Month						
		1	2	4	3	6	9	12	18	24	
Participant Point of Contact	Site Research	Site RT	Survey Center								

	Team (RT)									
Contact Information	X	X	X	X	X	X	X	X	X	X
EQ-5D ²⁵	X			X	X	X	X	X	X	X
10-PROMIS Global Health Short Form ²⁶	X			X	X			X	X	X
PROMIS-Pain Intensity	X	X	X							
Symptom Onset	X									
Additional Demographics*	X									
Treatment Satisfaction/Expectation	X			X	X**					
Gastrointestinal Quality of Life (GIQLI) ²⁷				X	X			X	X	X
Healthcare Utilization		X	X	X	X	X	X	X	X	X
Signs & Symptoms of Appendicitis		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Decision Regret Scale ²⁸				X	X			X		
Major Life Changes				X	X	X	X	X	X	X
Work Productivity Index		X	X	X	X					
Return to Work Information		X	X	X	X**					
Medication Use		X	X	X	X**					
Treatment Strategy Change		X	X	X						

*Includes the following topics: Demographics & Gender Identity, Caregiver Role, Instrumental Support, Employment/Student Status, Income, Pain Catastrophizing, Health Literacy, Social Support, Confidence in Treatment Success, Trust in Healthcare

**Only asked if the one month results have not normalized

The DCC performs early quality assurance checks by running REDCap data quality reports. These reports identify missing values for required fields, incorrect data type, range checks, outliers, hidden fields that contain values, and multiple choice fields with invalid values. Values that need to be corrected are brought to the attention of the research staff at that site.

Study Arms

Antibiotics Therapy Arm

Patients in the antibiotics treatment arm receive a minimum of 24 hours of treatment using an intravenous (IV) antibiotic formulation (administered in q8, q12, or q24 hour regimens) followed by oral antibiotics for a total of a 10-day antibiotic course. Patients are offered a treatment regimen of antibiotics based on guidelines published jointly by the Surgical Infection Society (SIS) and the Infectious Disease Society of America (IDSA) for intravenous antibiotics²⁹ and oral antibiotics based on *in vitro* activity against aerobic and anaerobic Gram-negative bacteria, practical experience with oral antibiotic regimens used to treat diverticulitis, and IDSA/SIS guidelines. The first dose of antibiotics is given in the ED at the time of diagnosis of appendicitis and a total

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3 outpatient regimen of antibiotics is an option for patients meeting ED discharge criteria.
4 Antibiotics are procured from the pharmacy by the patient as per usual clinical care.
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6 Appendectomy is recommended only if there is development of diffuse peritonitis,
7 development of septic shock³⁰, and/or worsening signs and symptoms of appendicitis
8 after 48 hours. The decision to perform an appendectomy in participants randomized to
9 antibiotics is made by the treating surgeon after consultation with the study clinical
10 research lead to confirm that the above criteria have been satisfied.

11 Standard discharge criteria are applied to those treated in the ED and those who
12 are admitted, and the criteria include tolerance of liquids, adequate pain control, and
13 improving clinical condition. All participants are contacted at 24-48 hours by the research
14 coordinator to review the study protocol for follow-up assessments.
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16 Follow-up with the clinical team is per usual care at each institution. Participants
17 in the antibiotics arm who return to any of the study sites during the follow-up period with
18 recurrent appendicitis are not re-randomized but are offered the choice of either
19 appendectomy or another antibiotic course, if treating surgeon agrees their recurrence
20 can be treated with either option.
21

22 Appendectomy Therapy Arm

23 All patients randomized to appendectomy receive preoperative antibiotics per
24 hospital standards for surgical infection prevention protocols. Appendectomy is
25 performed by an open or laparoscopic approach, depending on patient and surgeon
26 preference.
27

28 **Blinding and Randomization**

29 This is an un-blinded study as patients will know if they were randomized to
30 appendectomy or antibiotics. A separate data coordinating center (DCC) at the
31 University of Washington (UW) generates and maintains randomization lists for each
32 practice site. Using block randomization optimizes the chances of equal numbers of
33 subjects being randomized to each treatment arm and that treatment is balanced at
34 periodic enrollment intervals. Randomization is further stratified by the presence of
35 appendicolith. All other subgroups of interest will be sufficiently large such that the risk
36 of a meaningful imbalance in treatment groups by chance is unlikely. A web-based
37 portal provides the randomized treatment assignment.
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40 **Outcomes and Measures**

41 The primary outcome for the CODA trial is the EQ-5D index reported four weeks
42 after randomization. In addition, important clinical outcomes include major complications
43 and resolution of symptoms by four weeks, eventual appendectomy (due to failure in
44 clinical improvement, progression of disease severity or due to recurrent appendicitis),
45 pain, narcotic use, recurrent episodes of appendicitis, ED visits for abdominal pain/repeat
46 imaging, need for more complicated surgical procedure including laparoscopic converted
47 to open appendectomy and ileocectomy, rates of perforation, and rates of future small
48 bowel obstructions and hernia development are collected and will be reported through
49 two years. Complications in both treatment groups are tracked and adjudicated by an
50 independent safety monitor to determine their relation to the disease and treatment.
51 Secondary PROs include a measure of decisional regret, anxiety, additional QoL measures
52 (PROMIS-Global, Gastrointestinal Quality of Life Index (GIQLI)), days missed from work
53 or school, time in healthcare, measures of caregiver burden, and out-of-pocket
54 expenses.
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Sample Size

The sample size was calculated based on the difference in EQ-5D between the two treatment interventions. EQ-5D. (see Table 2) The EQ-5D QoL index ranges from 0 (worst QoL) to 1 (highest QoL), where anchor-based methods have shown that the minimally clinically important difference ranges 5%-10%.³¹ Based on data from a prior study of appendectomy with EQ-5D scores at 12 weeks,³² we estimate that the average EQ-5D for the participants randomized to appendectomy will be 0.90 with a standard deviation of 0.12. In order to assess QoL differences between interventions, a total of 1,552 patients will be enrolled, assuming a 90% follow-up at 4-weeks. This will give the study very high power (>99%) to rule out an EQ-5D difference between groups as small as 5% (if treatment differences of 0 to 2% are observed) and 80% power if a treatment difference of 3% is observed.²²

Table 2. Statistical power to declare non-inferiority on patient-reported quality of life, overall and by subgroup (Non-inferiority Margin, M = -5%, one-sided alpha=0.025).

Treatment Difference, Δ	Overall	Subgroups		
	N=1552	N=250	N=400	N=500
-3%	82.6%	-	-	-
-2%	99.4%	-	57.1%	67.9%
-1%	100%	62.4%	83.8%	91.4%
0%	100%	83.0%	96.4%	98.8%

Based on pilot data, stakeholder engagement, and we estimate a randomization rate of 30% of all potential patients. Based on current appendectomy volume at the hospitals participating in the trial, recruitment is planned for three years with potential for extension through four years.

Statistical Analysis

We will assess the EQ-5D at four weeks, using a linear regression model that adjusts for an indicator of randomized treatment group assignment and for all factors used to stratify randomization (i.e., recruitment site, presence of appendicolith). As recommended by the US Food and Drug Administration guidelines on clinical trial design, the estimated treatment effect and 97.5% one-sided confidence interval (CI) will be compared to the non-inferiority margin (M = -5%).³³⁻³⁶ We will conclude that antibiotics are non-inferior to appendectomy if the entire 97.5% one-sided CI is greater than M, as in example scenario A (Figure 1). This is equivalent to a one-sided (alpha=0.025) test of the null hypothesis $H_0: \Delta \leq -5\%$, for which Δ represents the difference in mean EQ-5D at 4-weeks comparing antibiotics-first to appendectomy-first treatment assignment. If the null hypothesis of $H_0: \Delta \leq -5\%$ is rejected at the final evaluation, then we will conduct a test of superiority to determine the level of statistical evidence supporting an alternative hypothesis $H_A: \Delta > 0\%$ (i.e., scenario B of Figure 1).

Important clinical endpoints (30-day major complications, days until resolution of symptoms, rates of perforated appendicitis, extent of operation and surgical complications, complications associated with antibiotics, hospital days, number of days using antibiotics beyond the initial treatment, clinic visits, and caregiver/patient "time in healthcare") will also be compared between ITT groups using regression models appropriate to each endpoint (e.g., linear, logistic, Poisson, or Cox proportional hazards regression models), along with a similar non-inferiority framework.

Secondary Analyses

We aim to include a heterogeneous population of patients and healthcare settings and plan to explore differences in treatment outcomes across subgroups of interest, including those with appendicolith, people with specific imaging findings including possible appendiceal perforation, those in different age groups (18-64 or ≥ 65), sex, and those whose outcomes may vary due to differences in work and insurance status, comorbidities, or social support. We will evaluate difference in treatment effectiveness based on modality of receipt of antibiotics (all outpatient vs inpatient/outpatient). We will separately assess treatment effect heterogeneity by adding to the primary outcome model an interaction term between the categorical subgroup variable of interest and the indicator of treatment. We will use a global likelihood ratio test to examine if the treatment effect differs between key subgroups of interest.

An intention-to-treat (ITT) approach will be applied in the primary analysis. We will conduct a secondary as-treated analysis of the primary outcome measure that appropriately accounts for patient- or provider-level characteristics found to be differentially represented among patients who start in the antibiotics arm and who undergo appendectomy before 24 hours of treatment, or patients who are randomized to appendectomy but refuse the procedure and continue on antibiotics. We will consider a two-stage approach for this as-treated analysis: 1) to identify subgroups that are likely to require appendectomy and therefore should not be considered good candidates for treatment with antibiotics as primary treatment strategy, and; 2) to estimate the complier average causal effect (CACE), which seeks to compare the outcomes of patients treated successfully in the antibiotic treatment arm (i.e., did not ultimately have surgery) with patients randomized to the appendectomy arm who are similar in their expected compliance to assigned treatment.³⁷⁻³⁹ We will use a maximum likelihood mixture modeling approach to identify the optimal comparison group from the control arm for observed compliers in the intervention arm. Secondary analyses of the primary outcome measures will include examining the entire trajectory of EQ-5D QoL measurements for each patient using linear mixed effects models for longitudinal data.⁴⁰ Lastly, a composite outcome metric (symptom resolution without complication) was used in the recently completed pilot trial and will be included as an exploratory measure.²² Because the composite outcome includes only clinical domains, and is relevant to both treatment groups, this may be a helpful measure for clinicians considering the two treatments.

Data Safety and Monitoring

Event Reporting:

Death, life threatening events and rehospitalization (other than for treatment of appendicitis) are classified as SAEs. Morbidity events (using modified definitions from NSQIP to accommodate non-operative care) are considered AEs. Adverse events (AEs), serious adverse events (SAEs) and appendectomy after starting antibiotic treatment are identified through 3 approaches; EMR review, patient surveys and through ad hoc reporting by any research or care team member. All SAEs are adjudicated by an independent safety monitor. SAEs and AEs are reviewed by the DSMB biannually (with the exception of death which is reported to the DSMB within 24-hours). An independent Data and Safety Monitoring Board (DSMB) reviews the accruing data to: 1) ensure that study conduct, enrollment, and patient follow-up is adequate; 2) ensure that there are no serious safety concerns; and 3) assess evidence related to patient-reported QoL. The analysis of accruing data is completed by the DCC and interim analysis is presented to the DSMB with the primary goal of monitoring safety outcomes by randomization group. Interim monitoring for SAE and AE will focus on the

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3 first four weeks of follow-up. The DSMB will conduct interim analyses at 12, 24, and 36
4 months.

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6 The CODA trial does not include a stopping rule if non-inferiority is met before
7 complete accrual or if it is determined that non-inferiority cannot be demonstrated in
8 interim analyses. We are not employing a stopping rule because there are important
9 secondary outcomes (e.g rate of eventual appendectomy, complications, subgroup
10 analysis) and understudied subgroups that require full enrollment.

11 12 **DISCUSSION**

13 Prior trials randomizing patients with appendicitis to antibiotics compared to
14 appendectomy focused on disease cure, with the primary outcome being the rate of
15 appendectomy among antibiotic-treated participants. Previous studies of more than 800
16 participants randomized to antibiotics suggested that the treatment did not increase the
17 rate of complications and offered as high as a 75% chance of avoiding appendectomy
18 within a year.^{6-9 12 41} What remains to be evaluated is the comparative effectiveness of
19 the two candidate treatments based on a comprehensive assessment of impact,
20 including the full range of clinical outcomes and PROs that matter most to patients.
21 CODA's pragmatic design aims to evaluate antibiotics in a heterogeneous population
22 and practice settings in a large randomized trial, with a parallel observational cohort to
23 assess selection bias. One of the greatest novelties of the CODA trial is its patient
24 centeredness, demonstrated both by the engagement of patients and other stakeholders
25 as partners in selecting the topic, designing the proposal, developing the protocol and
26 overseeing operations, as well as in the selection of a QoL endpoint for the primary
27 analysis.
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30 CODA was designed to directly inform patient and clinician decision-making in
31 the community and several pragmatic features were added to make sure it accounted for
32 the diverse aspects of the population, practice settings, and practices in the US. As a
33 pragmatic trial, CODA has limited exclusion criteria and incorporates the many ways
34 clinical care is delivered across sites of practice. The protocol allows patients in either
35 study arm to leave the healthcare setting as soon as standard discharge criteria are met,
36 including the possibility of completely outpatient care. CODA takes place in diverse
37 study sites (academic, private, public, community, and county hospitals) with patients
38 from a wide range of demographic and socioeconomic characteristics, including both
39 Spanish and English speakers. This enhances the generalizability of the findings, but
40 may compromise study fidelity if patients in any one group have differential treatment
41 preferences or prove more difficult to contact for follow-up. A downside to this approach
42 is that by including nearly all patients with appendicitis (including those with
43 appendicolith and radiographic findings of perforation who may be at higher risk for
44 requiring an appendectomy) and those undergoing total outpatient antibiotics (which
45 clinicians have less experience with) there is a risk of subgroups with very different
46 outcomes from the broader population and a skewing of the average study results. Using
47 Thorpe's PRECIS rubric for pragmatic trials, the proposed study is considered highly
48 pragmatic, intended to improve the generalization and precision of decision-making
49 beyond the prior randomized studies.⁴²
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52 The results from the European trials of antibiotics have not significantly changed
53 care delivery in the US and have been met with resistance, in part due to the evidence
54 gaps cited earlier and concern about the fate of patients with recurrent disease.⁴³
55 American patients may also have different expectations and resources that influence
56 perception of treatment success and satisfaction with treatments. One particular protocol
57 component of the European trials that may make them less applicable to the US
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experience is that prior studies all required an in-hospital convalescence for a fixed period of time for both treatment arms that is double the length of stay that the average US patient experiences. CODA builds on the successful experience of emergency medicine clinicians to manage patients with potentially serious infections as outpatients using risk-stratification and long-acting parenteral antibiotics (e.g., diverticulitis) and its effectiveness will be tested in different practice settings and populations. This novel treatment alternative offers avoidance of hospital admission and may substantially reduce costs compared to surgical treatment,

Stakeholder input is a key component of the emerging field of patient-centered outcomes research. However, including several types of stakeholders (patients, physicians, payers, and purchasers) does not always result in consensus. The selection of an appropriate analytic outcome for the trial was an example. While prior studies focused on clinical outcome (e.g., rates of appendectomy and surgical complications), patient advisors recognized that these outcome measures are specific to only one treatment arm (and to people treated with antibiotics who proceed to appendectomy) and that standardized measurements of quality of life would be applicable to both and had yet to be rigorously assessed. The EQ-5D has been used in prior studies of appendectomy, but never in comparisons of these two treatments.³² Using the EQ-5D as a primary outcome measure was highly relevant to many, but not all, patients. There is a possibility that the primary analytic outcome analysis (non-inferiority of the EQ-5D) could be positive, but other outcome domains might not be aligned. For this reason, multiple secondary analyses and exploratory endpoints have been selected a priori. Evidence in the field of decision-making suggests that patients want information on multiple domains, but we recognize that multiple outcome domains may also add confusion to interpretation of results and implementation in future practice.

As in all trials, patients are not required to stay in the treatment arms they are assigned to (non-adherence or crossover); for example, select patients in the antibiotics arm might not be willing to receive 24 hours of antibiotics and opt for an appendectomy despite not meeting clinical trial protocol recommendations, or patients randomized to appendectomy might refuse surgery. While the main analytic approach is an intention to treat framework, careful as-treated and secondary data analyses may be helpful in accounting for such non-adherence/crossover.⁴⁴ Detry recommends both an ITT and a careful as-treated analysis to address crossovers in non-inferiority trials where non-adherence or crossover is present.⁴⁵ A simple as-treated analysis is problematic because of potential differences in demographic or clinical characteristics that introduce bias in as-treated group comparisons. Our analytic approach proposed involves a two-stage as-treated analysis and potentially will yield conclusions that differ from ITT analysis. However, the ITT results will be considered the primary analysis and are robustly valid since they only depend on randomization and do not depend on model assumptions required for observational comparisons.⁴⁵

CODA began recruitment in the Summer/Fall of 2016 and now involves eight hospitals in Washington and California with two hospitals planned to begin recruitment in 2017. It is possible that not all clinical sites will continue to contribute patients throughout the entire recruitment period (projected to be 3-4 years). Sub-studies and ancillary studies are being proposed to focus on biomarkers, economic analysis, longer-term results, and other predictors of outcome.

In conclusion, the CODA trial was designed to address critical knowledge gaps related to the treatment of appendicitis with antibiotics compared with appendectomy. CODA's stakeholder-informed design and operations, pragmatic design, and inclusion of an innovative approach to outpatient antibiotics aim to inform choices in care for this common condition, and planned subgroup analyses allow for improved decision-making.

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Author Contributions: Dr. Davidson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final manuscript and are accountable for the followings aspects of the work:

Study concept and design: GD, DF, DT, LK, DL, EW, BC, SM, PH
 Acquisition of data: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH, AE, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM
 Analysis and interpretation of data: GD, DF, DT, LK, DL, EW, BC, SM, PH, EC
 Drafting of the manuscript: GD, DF, DT, EW, AK, AE, DL
 Critical revision of the manuscript for important intellectual content: GD, DF, DT, EW, BC, SM, PH, EC
 Final approval of the manuscript: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH, AE, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM
 Statistical analysis: PH, BC, SM, DF, GD, DT
 Administrative, technical, or material support: EW, EC, AK, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM
 Study supervision: GD, DF, DT, LK, DL, BB, FF, SS, AK, EC, EW, BC, SM, PH, AE, DD, AK, HE, JY, KM, ID, KC, KM, BT, CF, DS, RT, EL, AS, GM

All authors have read and understood BMJ policy on declaration of interests and declare that have no competing interests. Data will be available per PCORI's Data Access and Data Sharing Policy.

Ethics and Dissemination: This trial was approved by the University of Washington's Human Subjects Division on April 21, 2016 (Version 3.5). The University of Washington serves as the IRB of record for the following study sites: University of Washington Medical Center, Harborview Medical Center, Virginia Mason Medical Center, and Madigan Army Medical Center. Western IRB is the overseeing IRB for Swedish-First Hill (approved July 8, 2016) and Providence Regional Medical Center (approved July 1, 2016). UCLA-Olive View (approved June 12, 2016) and UCLA-Harbor (approved March 4, 2016) are both regulated by their respective institutional IRBs.

Trial Registration: Clinicaltrials.org registered on: June 10, 2016 (NCT02800785)

Figure Legends:

Figure 1. Example study conclusions in the CODA trial. There are four possible study conclusions. A: The observed treatment effect (black circle) of antibiotics is almost zero and the 97.5% one-sided confidence interval (CI, arrow) does not overlap the non-inferiority margin of -5%, indicating antibiotics is a non-interior strategy. B: The observed treatment effect of antibiotics is more than 2.5% better than appendectomy and the CI does not include 0, indicating that antibiotics are superior. C: The observed treatment effect of antibiotics is 2.5% worse than appendectomy but the CI includes -5%, so non-inferiority cannot be claims. D: The observed treatment effect of antibiotics is more than 5% worse than appendectomy, indicating that antibiotics are inferior.

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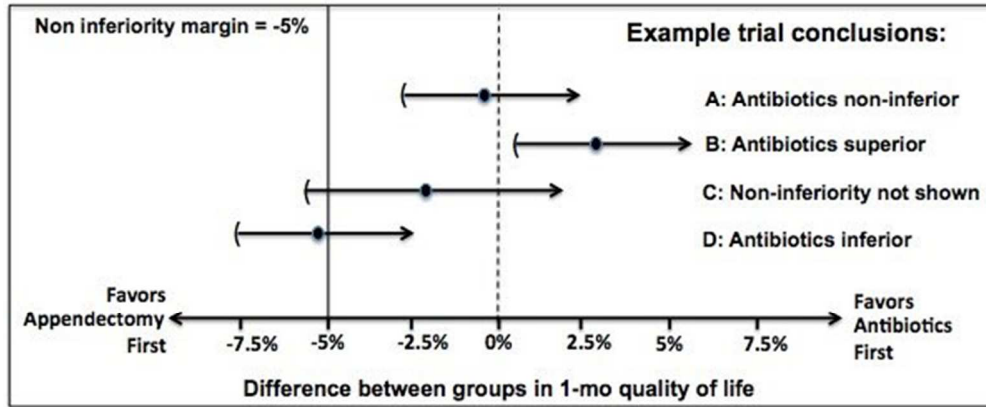


Figure 1

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Peer review only

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____
	5b	Name and contact information for the trial sponsor	_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant
4 rationale studies (published and unpublished) examining benefits and harms for each intervention _____
5

6

7 6b Explanation for choice of comparators _____
8

9 Objectives 7 Specific objectives or hypotheses _____
10

11 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),
12 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____
13

14 **Methods: Participants, interventions, and outcomes**

15

16

17 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will
18 be collected. Reference to where list of study sites can be obtained _____
19

20 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and
21 individuals who will perform the interventions (eg, surgeons, psychotherapists) _____
22

23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be
24 administered _____
25

26 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose
27 change in response to harms, participant request, or improving/worsening disease) _____
28

29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence
30 (eg, drug tablet return, laboratory tests) _____
31

32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____
33

34

35 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
36 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
37 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
38 efficacy and harm outcomes is strongly recommended _____
39

40

41 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for
42 participants. A schematic diagram is highly recommended (see Figure) _____
43

1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____
 2 clinical and statistical assumptions supporting any sample size calculations

3
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____
 5
 6

7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

9
 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 13 or assign interventions
 14
 15

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism
 19
 20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____
 22 interventions
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____
 25 assessors, data analysts), and how
 26
 27

28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____
 29 allocated intervention during the trial
 30
 31

32 **Methods: Data collection, management, and analysis**

33
 34 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____
 35 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 37 Reference to where data collection forms can be found, if not in the protocol
 38
 39

40 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____
 41 collected for participants who discontinue or deviate from intervention protocols
 42
 43
 44

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	_____
2			(eg, double data entry; range checks for data values). Reference to where details of data management	
3			procedures can be found, if not in the protocol	
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	_____
6			statistical analysis plan can be found, if not in the protocol	
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	_____
11			statistical methods to handle missing data (eg, multiple imputation)	
12				
13				
14				
15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	_____
18			whether it is independent from the sponsor and competing interests; and reference to where further details	
19			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	
20			needed	
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	_____
23			results and make the final decision to terminate the trial	
24				
25				
26	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	_____
27			events and other unintended effects of trial interventions or trial conduct	
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	_____
30			from investigators and the sponsor	
31				
32				
33	Ethics and dissemination			
34				
35	Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____
36	approval			
37				
38	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	_____
39	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
40			regulators)	
41				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and	_____
2			how (see Item 32)	
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	_____
5			studies, if applicable	
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained	_____
8			in order to protect confidentiality before, during, and after the trial	
9				
10	Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____
11	interests			
12				
13				
14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that	_____
15			limit such access for investigators	
16				
17	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	_____
18	trial care		participation	
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals,	_____
21			the public, and other relevant groups (eg, via publication, reporting in results databases, or other data	
22			sharing arrangements), including any publication restrictions	
23				
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
28				
29				
30	Appendices			
31				
32	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
33	materials			
34				
35	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	_____
36	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
37				

38
39 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
40 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
41 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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