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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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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 patients with uncomplicated appendicitis can be treated safely with antibiotics. A minority of patients eventually undergo appendectomy within a year, with 10-15% failing to respond in the initial period and a similar proportion with suspected recurrent episodes requiring appendectomy. Nearly all patients with uncomplicated 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 uncomplicated appendicitis (AUA) 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 AUA. 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.

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

Strengths and Limitations of this Study:

- CODA is a randomized, pragmatic, multi-site non-inferiority trial that aims to determine if antibiotics are as good as appendectomy in treating acute uncomplicated appendicitis.
- The primary analytic outcome is quality of life at four weeks and clinical adverse events, appendicitis signs and symptoms, rate of eventual appendectomy, anxiety, decisional regret, return to work/school, work productivity, and healthcare utilization will also be compared. Exploratory analyses will identify subpopulations at higher risk of eventual appendectomy in the antibiotic treatment arm.
- Stakeholders including patients, clinicians, and leaders in healthcare and industry provided input that influenced the study design, protocol, patient-facing study materials, and clinical and patient reported outcomes.

- 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 Strepotomycin 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,

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

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

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

TRIAL DESIGN

Stakeholder Input in Design, Informed Consent, and Protocol

A central feature of the CODA trial is its engagement of stakeholders in study conception, design, and implementation of the trial.[23] The Stakeholder Coordinating Center (SCC), established as a formal core within the study infrastructure, facilitates all engagement activities. The SCC engages representatives from the patient population of interest (those at risk for or who have had acute uncomplicated appendicitis), clinicians who are involved in appendicitis treatment (including emergency physicians, nurses, and

surgeons), leaders of professional societies (American College of Surgeons and American College of Emergency Physicians), representatives of Accountable Care Organizations, policy-makers, insurers and payers, researchers, and leaders from large, self-insured employers. Specific areas of protocol development informed by the SCC included selecting primary and secondary outcomes. In addition to the routine clinical metrics that are assessed in any study of acute uncomplicated appendicitis treatment, other outcome measures important to patients (anxiety, quality of life, time away from work, out of pocket expenses) and employers (time away from work and productivity at work) were included. Stakeholder input was particularly helpful in determining the primary analytic outcome, helping weigh the prior evidence showing no difference in rates of complications with an outcome metric that would "sum up" the impact of both treatments on the care experience of patients.

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

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

Study Aims and Hypothesis

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

Study population

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

Exclusion Criteria

- Inability to participate in follow-up (i.e., incarcerated, travel without access to phone, email)
- Contraindication to one of the study treatment arms:
    - Septic shock
    - Phlegmon for which surgery would not be recommended or diffuse peritonitis for which antibiotics alone would not be recommended

- 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 antibiotics[29] 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

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 delegate 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. [36-38] 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.[39] 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 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

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

The results from the European trials of antibiotics have not significantly changed care delivery in the US and have been met with resistance, in part due to the evidence gaps cited earlier and concern about the fate of patients with recurrent disease.[43] American patients may also have different expectations and resources that influence perception of treatment success and satisfaction with treatments. One particular protocol component of the European trials that may make them less applicable to the US 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.[31] 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 recommendations for antibiotic arm treatment failure, 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.

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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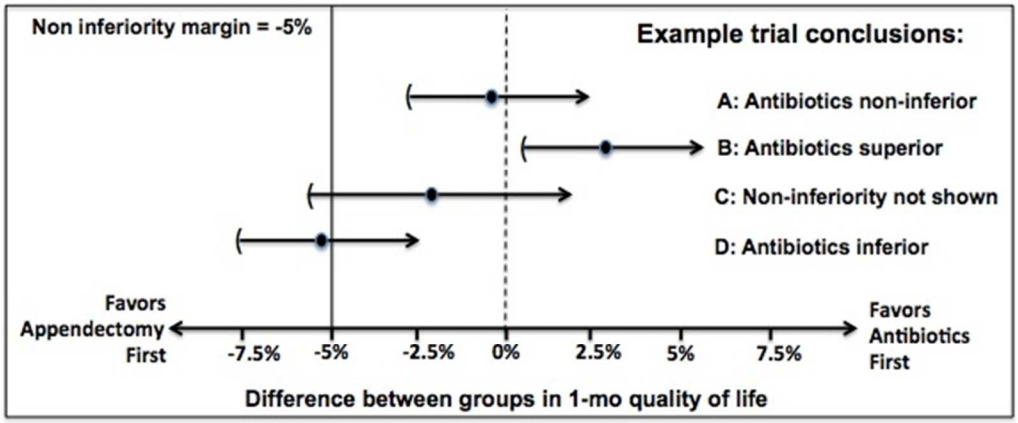
References

1. Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132(5):910-25.
2. Chang DC, Shiozawa A, Nguyen LL, et al. Cost of inpatient care and its association with hospital competition. *J Am Coll Surg* 2011;212(1):12-9. doi: 10.1016/j.jamcollsurg.2010.09.014
3. Dieleman JL, Baral R, Birger M, et al. US Spending on Personal Health Care and Public Health, 1996-2013. *JAMA* 2016;316(24):2627-46. doi: 10.1001/jama.2016.16885
4. Coldrey E. Five years of conservative treatment of acute appendicitis. *J Int Coll Surg* 1959;32:255-61.

5. Wojciechowicz KH, Hoffkamp HJ, van Hulst RA. Conservative treatment of acute appendicitis: an overview. *Int Marit Health* 2010;62(4):265-72.
6. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 2006;30(6):1033-7. doi: 10.1007/s00268-005-0304-6
7. Hansson J, Korner U, Khorram-Manesh A, et al. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 2009;96(5):473-81. doi: 10.1002/bjs.6482
8. Eriksson S, Granstrom L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995;82(2):166-9.
9. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377(9777):1573-9. doi: 10.1016/S0140-6736(11)60410-8
10. Mason RJ, Moazzez A, Sohn H, et al. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect (Larchmt)* 2012;13(2):74-84. doi: 10.1089/sur.2011.058
11. Findlay JM, Kafsi JE, Hammer C, et al. Nonoperative Management of Appendicitis in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Coll Surg* 2016;223(6):814-24 e2. doi: 10.1016/j.jamcollsurg.2016.09.005
12. Salminen P, Paajanen H, Rautio T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA* 2015;313(23):2340-8. doi: 10.1001/jama.2015.6154
13. Ehlers AP, Talan DA, Moran GJ, et al. Evidence for an Antibiotics-First Strategy for Uncomplicated Appendicitis in Adults: A Systematic Review and Gap Analysis. *J Am Coll Surg* 2016;222(3):309-14. doi: 10.1016/j.jamcollsurg.2015.11.009
14. Anderson JE, Bickler SW, Chang DC, et al. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. *World J Surg* 2012;36(12):2787-94. doi: 10.1007/s00268-012-1749-z
15. Felson B. Appendical calculi; incidence and clinical significance. *Surgery* 1949;25(5):734-7.
16. Shindoh J, Niwa H, Kawai K, et al. Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. *J Gastrointest Surg* 2010;14(2):309-14. doi: 10.1007/s11605-009-1094-1
17. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg* 2015;50(11):1893-7. doi: 10.1016/j.jpedsurg.2015.07.008
18. Gaskill CE SV, Carnell J, Hippe DS, Bhargava P, Flum DR, Davidson GH. Use of Computed Tomography to Determine Perforation in Patients with Acute Appendicitis. *Current Problems in Diagnostic Radiology* 2016 doi: http://dx.doi.org/10.1067/j.cpradiol.2016.12.002 [published Online First: December 7, 2016]
19. O'Leary DP, Lynch N, Clancy C, et al. International, Expert-Based, Consensus Statement Regarding the Management of Acute Diverticulitis. *JAMA Surg* 2015;150(9):899-904. doi: 10.1001/jamasurg.2015.1675
20. Vennix S, Morton DG, Hahnloser D, et al. Systematic review of evidence and consensus on diverticulitis: an analysis of national and international guidelines. *Colorectal Dis* 2014;16(11):866-78. doi: 10.1111/codi.12659

21. Morris AM, Regenbogen SE, Hardiman KM, et al. Sigmoid diverticulitis: a systematic review. *JAMA* 2014;311(3):287-97. doi: 10.1001/jama.2013.282025
22. Talan DA SD, Mower WR, Krishnadasan A, Jude CM, Amii R, DeUgarte DA, Wu JX, Pathmarajah K, Morim A, Moran GJ, for the Olive View-UCLA Appendicitis Study Group. Antibiotics first versus surgery for appendicitis: A US pilot randomized controlled trial allowing outpatient antibiotic management. *Ann Emerg Med* 2016 doi: (doi:10.1016/j.annemergmed.2016.08.446)
23. Ehlers AP, Davidson GH, Bizzell BJ, et al. Engaging Stakeholders in Surgical Research: The Design of a Pragmatic Clinical Trial to Study Management of Acute Appendicitis. *JAMA Surg* 2016;151(6):580-2. doi: 10.1001/jamasurg.2015.5531
24. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010
25. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43.
26. Amtmann D, Cook KF, Johnson KL, et al. The PROMIS initiative: involvement of rehabilitation stakeholders in development and examples of applications in rehabilitation research. *Arch Phys Med Rehabil* 2011;92(10 Suppl):S12-9. doi: 10.1016/j.apmr.2011.04.025
27. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995;82(2):216-22.
28. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making* 2003;23(4):281-92.
29. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11(1):79-109. doi: 10.1089/sur.2009.9930
30. Le QA, Doctor JN, Zoellner LA, et al. Minimal clinically important differences for the EQ-5D and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized Preference Trial (DRPT). *Health Qual Life Outcomes* 2013;11:59. doi: 10.1186/1477-7525-11-59
31. Koumarelas K, Theodoropoulos GE, Spyropoulos BG, et al. A prospective longitudinal evaluation and affecting factors of health related quality of life after appendectomy. *Int J Surg* 2014;12(8):848-57. doi: 10.1016/j.ijsu.2014.06.015
32. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. *Stat Med* 1999;18(15):1905-42.
33. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308(24):2594-604. doi: 10.1001/jama.2012.87802
34. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309(8):814-22. doi: 10.1001/jama.2013.879
35. Turner L, Shamseer L, Altman DG, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev* 2012;11:MR000030. doi: 10.1002/14651858.MR000030.pub2

36. Angrist JD, Imbens GW. 2-Stage Least-Squares Estimation of Average Causal Effects in Models with Variable Treatment Intensity. *J Am Stat Assoc* 1995;90(430):431-42. doi: Doi 10.2307/2291054
37. Little RJ, Yau LHY. Statistical techniques for analyzing data from prevention trials: Treatment of no-shows using Rubin's causal model. *Psychol Methods* 1998;3(2):147-59. doi: Doi 10.1037/1082-989x.3.2.147
38. Bloom HS. Accounting for No-Shows in Experimental Evaluation Designs. *Evaluation Rev* 1984;8(2):225-46. doi: Doi 10.1177/0193841x8400800205
39. Diggle PJ HP, Liang KY, Zeger SL. Analysis of Longitudinal Data. Second Edition ed2002.
40. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):801-10. doi: 10.1001/jama.2016.0287
41. Turhan AN, Kapan S, Kutukcu E, et al. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2009;15(5):459-62.
42. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ* 2009;180(10):E47-57. doi: 10.1503/cmaj.090523
43. Khalil M, Rhee P, Jokar TO, et al. Antibiotics for appendicitis! Not so fast. *J Trauma Acute Care Surg* 2016;80(6):923-32. doi: 10.1097/TA.0000000000001030
44. Sitlani CM, Heagerty PJ, Blood EA, et al. Longitudinal structural mixed models for the analysis of surgical trials with noncompliance. *Stat Med* 2012;31(16):1738-60. doi: 10.1002/sim.4510
45. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. *JAMA* 2014;312(1):85-6. doi: 10.1001/jama.2014.7523



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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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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.

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

Strengths and Limitations of this Study:

- CODA is a randomized, pragmatic, multi-site non-inferiority trial that aims to determine if antibiotics are as good as appendectomy in treating most cases of acute appendicitis.
- The primary analytic outcome is quality of life at four weeks and clinical adverse events, appendicitis signs and symptoms, rate of eventual appendectomy, anxiety, decisional regret, return to work/school, work productivity, and healthcare utilization will also be compared. Exploratory analyses will identify subpopulations at higher risk of eventual appendectomy in the antibiotic treatment arm.
- Stakeholders including patients, clinicians, and leaders in healthcare and industry provided input that influenced the study design, protocol, patient-facing study materials, and clinical and patient reported outcomes.

- 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 Strepotomycin 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 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 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,

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

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

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

TRIAL DESIGN

Stakeholder Input in Design, Informed Consent, and Protocol

A central feature of the CODA trial is its engagement of stakeholders in study conception, design, and implementation of the trial.[23] The Stakeholder Coordinating Center (SCC), established as a formal core within the study infrastructure, facilitates all

engagement activities. The SCC engages representatives from the patient population of interest (those at risk for or who have had appendicitis), clinicians who are involved in appendicitis treatment (including emergency physicians, nurses, and surgeons), leaders of professional societies (American College of Surgeons and American College of Emergency Physicians), representatives of Accountable Care Organizations, policy-makers, insurers and payers, researchers, and leaders from large, self-insured employers. Specific areas of protocol development informed by the SCC included selecting primary and secondary outcomes. In addition to the routine clinical metrics that are assessed in any study of appendicitis treatment, other outcome measures important to patients (anxiety, quality of life, time away from work, out of pocket expenses) and employers (time away from work and productivity at work) were included. Stakeholder input was particularly helpful in determining the primary analytic outcome, helping weigh the prior evidence showing no difference in rates of complications with an outcome metric that would "sum up" the impact of both treatments on the care experience of patients.

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

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

Study Aims and Hypothesis

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

Study population

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

Exclusion Criteria

- Inability to participate in follow-up (i.e., incarcerated, travel without access to phone, email)
- Contraindication to one of the study treatment arms:

- 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=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 antibiotics[29] 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[30], 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 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

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 delegate 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 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

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

The results from the European trials of antibiotics have not significantly changed care delivery in the US and have been met with resistance, in part due to the evidence gaps cited earlier and concern about the fate of patients with recurrent disease.[43] American patients may also have different expectations and resources that influence perception of treatment success and satisfaction with treatments. One particular protocol component of the European trials that may make them less applicable to the US 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.

References

1. Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132(5):910-25.
2. Chang DC, Shiozawa A, Nguyen LL, et al. Cost of inpatient care and its association with hospital competition. *J Am Coll Surg* 2011;212(1):12-9. doi: 10.1016/j.jamcollsurg.2010.09.014
3. Dieleman JL, Baral R, Birger M, et al. US Spending on Personal Health Care and Public Health, 1996-2013. *JAMA* 2016;316(24):2627-46. doi: 10.1001/jama.2016.16885
4. Coldrey E. Five years of conservative treatment of acute appendicitis. *J Int Coll Surg* 1959;32:255-61.
5. Wojciechowicz KH, Hoffkamp HJ, van Hulst RA. Conservative treatment of acute appendicitis: an overview. *Int Marit Health* 2010;62(4):265-72.
6. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 2006;30(6):1033-7. doi: 10.1007/s00268-005-0304-6
7. Hansson J, Korner U, Khorram-Manesh A, et al. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 2009;96(5):473-81. doi: 10.1002/bjs.6482
8. Eriksson S, Granstrom L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995;82(2):166-9.
9. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377(9777):1573-9. doi: 10.1016/S0140-6736(11)60410-8
10. Mason RJ, Moazzez A, Sohn H, et al. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect (Larchmt)* 2012;13(2):74-84. doi: 10.1089/sur.2011.058
11. Findlay JM, Kafsi JE, Hammer C, et al. Nonoperative Management of Appendicitis in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Coll Surg* 2016;223(6):814-24 e2. doi: 10.1016/j.jamcollsurg.2016.09.005
12. Salminen P, Paajanen H, Rautio T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA* 2015;313(23):2340-8. doi: 10.1001/jama.2015.6154
13. Ehlers AP, Talan DA, Moran GJ, et al. Evidence for an Antibiotics-First Strategy for Uncomplicated Appendicitis in Adults: A Systematic Review and Gap Analysis. *J Am Coll Surg* 2016;222(3):309-14. doi: 10.1016/j.jamcollsurg.2015.11.009
14. Anderson JE, Bickler SW, Chang DC, et al. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. *World J Surg* 2012;36(12):2787-94. doi: 10.1007/s00268-012-1749-z
15. Felson B. Appendical calculi; incidence and clinical significance. *Surgery* 1949;25(5):734-7.
16. Shindoh J, Niwa H, Kawai K, et al. Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. *J Gastrointest Surg* 2010;14(2):309-14. doi: 10.1007/s11605-009-1094-1

17. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg* 2015;50(11):1893-7. doi: 10.1016/j.jpedsurg.2015.07.008
18. Gaskill CE SV, Carnell J, Hippe DS, Bhargava P, Flum DR, Davidson GH. Use of Computed Tomography to Determine Perforation in Patients with Acute Appendicitis. *Current Problems in Diagnostic Radiology* 2016 doi: http://dx.doi.org/10.1067/j.cpradiol.2016.12.002 [published Online First: December 7, 2016]
19. O'Leary DP, Lynch N, Clancy C, et al. International, Expert-Based, Consensus Statement Regarding the Management of Acute Diverticulitis. *JAMA Surg* 2015;150(9):899-904. doi: 10.1001/jamasurg.2015.1675
20. Vennix S, Morton DG, Hahnloser D, et al. Systematic review of evidence and consensus on diverticulitis: an analysis of national and international guidelines. *Colorectal Dis* 2014;16(11):866-78. doi: 10.1111/codi.12659
21. Morris AM, Regenbogen SE, Hardiman KM, et al. Sigmoid diverticulitis: a systematic review. *JAMA* 2014;311(3):287-97. doi: 10.1001/jama.2013.282025
22. Talan DA SD, Mower WR, Krishnadasan A, Jude CM, Amii R, DeUgarte DA, Wu JX, Pathmarajah K, Morim A, Moran GJ, for the Olive View-UCLA Appendicitis Study Group. Antibiotics first versus surgery for appendicitis: A US pilot randomized controlled trial allowing outpatient antibiotic management. *Ann Emerg Med* 2016 doi: (doi:10.1016/j.annemergmed.2016.08.446)
23. Ehlers AP, Davidson GH, Bizzell BJ, et al. Engaging Stakeholders in Surgical Research: The Design of a Pragmatic Clinical Trial to Study Management of Acute Appendicitis. *JAMA Surg* 2016;151(6):580-2. doi: 10.1001/jamasurg.2015.5531
24. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010
25. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43.
26. Amtmann D, Cook KF, Johnson KL, et al. The PROMIS initiative: involvement of rehabilitation stakeholders in development and examples of applications in rehabilitation research. *Arch Phys Med Rehabil* 2011;92(10 Suppl):S12-9. doi: 10.1016/j.apmr.2011.04.025
27. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995;82(2):216-22.
28. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making* 2003;23(4):281-92.
29. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11(1):79-109. doi: 10.1089/sur.2009.9930
30. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):801-10. doi: 10.1001/jama.2016.0287
31. Le QA, Doctor JN, Zoellner LA, et al. Minimal clinically important differences for the EQ-5D and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized Preference Trial (DRPT). *Health Qual Life Outcomes* 2013;11:59. doi: 10.1186/1477-7525-11-59

32.Koumarelas K, Theodoropoulos GE, Spyropoulos BG, et al. A prospective longitudinal evaluation and affecting factors of health related quality of life after appendectomy. *Int J Surg* 2014;12(8):848-57. doi: 10.1016/j.ijsu.2014.06.015
33. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. *Stat Med* 1999;18(15):1905-42.
34. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308(24):2594-604. doi: 10.1001/jama.2012.87802
35. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309(8):814-22. doi: 10.1001/jama.2013.879
36. Turner L, Shamseer L, Altman DG, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev* 2012;11:MR000030. doi: 10.1002/14651858.MR000030.pub2
37. Angrist JD, Imbens GW. 2-Stage Least-Squares Estimation of Average Causal Effects in Models with Variable Treatment Intensity. *J Am Stat Assoc* 1995;90(430):431-42. doi: Doi 10.2307/2291054
38. Little RJ, Yau LHY. Statistical techniques for analyzing data from prevention trials: Treatment of no-shows using Rubin's causal model. *Psychol Methods* 1998;3(2):147-59. doi: Doi 10.1037/1082-989x.3.2.147
39. Bloom HS. Accounting for No-Shows in Experimental Evaluation Designs. *Evaluation Rev* 1984;8(2):225-46. doi: Doi 10.1177/0193841x8400800205
40. Diggle PJ HP, Liang KY, Zeger SL. Analysis of Longitudinal Data. Second Edition ed2002.
41. Turhan AN, Kapan S, Kutukcu E, et al. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2009;15(5):459-62.
42. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ* 2009;180(10):E47-57. doi: 10.1503/cmaj.090523
43. Khalil M, Rhee P, Jokar TO, et al. Antibiotics for appendicitis! Not so fast. *J Trauma Acute Care Surg* 2016;80(6):923-32. doi: 10.1097/TA.0000000000001030
44. Sitlani CM, Heagerty PJ, Blood EA, et al. Longitudinal structural mixed models for the analysis of surgical trials with noncompliance. *Stat Med* 2012;31(16):1738-60. doi: 10.1002/sim.4510
45. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. *JAMA* 2014;312(1):85-6. doi: 10.1001/jama.2014.7523

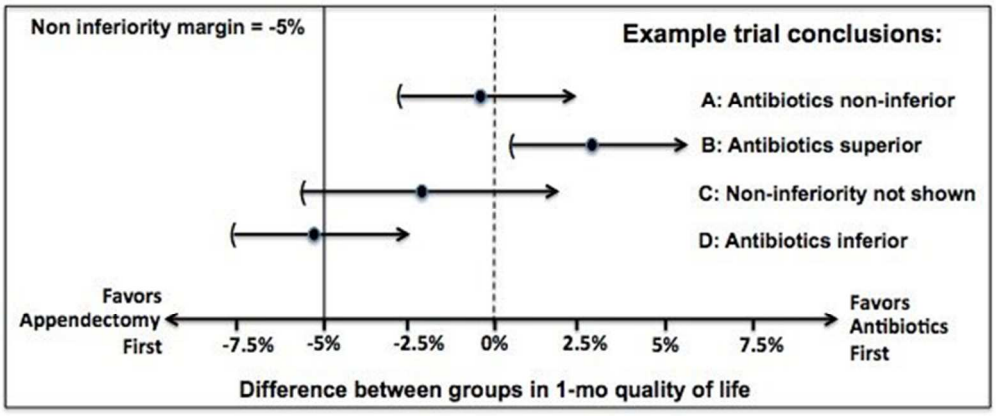

Figure 1

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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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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

the treatment of choice for 120 years, the successful use of antibiotics was reported both in a series of over 500 patients treated with Strepotomycin 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 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 post-interventional complications (reported as clinical wound infections, incisional hernia, abdominal pain or obstructive symptoms) in the antibiotics group requiring intervention 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, no study used a validated patient-reported outcome (PRO) tool to measure the patient's experience in a standardized fashion. Other important outcomes to patients such as impact on work and school productivity, lingering symptoms, decisional regret, and healthcare burden (such as emergency room care or future imaging) were not included in prior studies. Furthermore, prior studies regimented care in ways that are not consistent with care in the United States (US), such as requiring several days of in-hospital convalescence. These limitations may explain the infrequent use of antibiotics as the primary treatment for appendicitis in the US.[14]

In addition to the need to address these limitations, there are additional, unresolved questions that make a larger, more definitive study of this treatment question important. First, there may be important subgroups of people with acute appendicitis who experience the treatment differentially. These might include older patients, who are at higher risk for surgical complications, those with possible appendiceal perforation detected on imaging, or those with an appendicolith. The association between appendicolith and worse outcomes with antibiotics is unclear. Appendicoliths are found in up to 20% of appendicitis cases; a similar proportion is also described in autopsy studies of normal appendices.[15] In several pediatric studies and at least one adult study, appendicolith seemed to be associated with eventual appendectomy; however, since

many trials did not include standardized imaging or criteria for requiring appendectomy following antibiotic therapy for appendicitis, it is unclear if the presence of an appendicolith actually confers a greater risk.[16 17] There is currently no standard definition of "complicated" disease. In the United States, usual care for appendiceal abscess or phegmon (inflammation so significant that surgeons are concerned for associated surgical morbidity) is antibiotics with consideration for interval appendectomy. Optimal treatment strategies for preoperative radiographic findings of appendiceal perforation is an area of controversy. The use of radiologic imaging to accurately determine perforation is limited; in prior randomized trials, patients with perforation were likely to have been inadvertently included due to a lack of imaging.[18] Finally, the European studies mandated the use of inpatient antibiotics at a time when there was a growing use of outpatient antibiotic regimens for similar conditions, such as acute diverticulitis.[19-21] A recently completed, pilot randomized trial in the US found that 14 of 15 adults randomized to antibiotics could successfully be discharged from the emergency department (ED) and receive all their care as outpatients, resolving their symptoms of acute appendicitis.[22] One of the remaining questions is whether this total outpatient approach to antibiotics would be as good as appendectomy in usual practice.

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

TRIAL DESIGN

Stakeholder Input in Design, Informed Consent, and Protocol

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

Because appendectomy was considered the standard and nearly universal therapy in the US, advisors recommended a study that considered the non-inferiority of the antibiotics-first strategy. As one advisor said, "the burden of proof is on the

antibiotics treatment approach to demonstrate that it is as good as appendectomy" (or not inferior by more than a small margin). Advisors also favored a non-inferiority framework because the larger size required for this design would also allow for multiple planned sub-group analyses for patient groups of interest and the possibility that superiority of the PRO measure might be demonstrated. Lastly, advisors suggested a parallel observational cohort to assess for potential selection bias for patients who declined randomization.

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

Study Aims and Hypothesis

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

Study population

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

Exclusion Criteria

- Inability to participate in follow-up (i.e., incarcerated, travel without access to phone, email)
- Contraindication to one of the study treatment arms:
    - Septic shock (evidence of severe sepsis or septic shock includes new presumed sepsis-related organ dysfunction, elevated lactate, and/or fluid unresponsive hypotension)
    - 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=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	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 antibiotics[29] 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[30], 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. In addition, 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 are collected and will be reported 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 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 delegate 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

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

The results from the European trials of antibiotics have not significantly changed care delivery in the US and have been met with resistance, in part due to the evidence gaps cited earlier and concern about the fate of patients with recurrent disease.[43] American patients may also have different expectations and resources that influence perception of treatment success and satisfaction with treatments. One particular protocol component of the European trials that may make them less applicable to the US

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.

References

1. Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132(5):910-25.
2. Chang DC, Shiozawa A, Nguyen LL, et al. Cost of inpatient care and its association with hospital competition. *J Am Coll Surg* 2011;212(1):12-9. doi: 10.1016/j.jamcollsurg.2010.09.014
3. Dieleman JL, Baral R, Birger M, et al. US Spending on Personal Health Care and Public Health, 1996-2013. *JAMA* 2016;316(24):2627-46. doi: 10.1001/jama.2016.16885
4. Coldrey E. Five years of conservative treatment of acute appendicitis. *J Int Coll Surg* 1959;32:255-61.
5. Wojciechowicz KH, Hoffkamp HJ, van Hulst RA. Conservative treatment of acute appendicitis: an overview. *Int Marit Health* 2010;62(4):265-72.
6. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 2006;30(6):1033-7. doi: 10.1007/s00268-005-0304-6
7. Hansson J, Korner U, Khorram-Manesh A, et al. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 2009;96(5):473-81. doi: 10.1002/bjs.6482
8. Eriksson S, Granstrom L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995;82(2):166-9.
9. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377(9777):1573-9. doi: 10.1016/S0140-6736(11)60410-8
10. Mason RJ, Moazzez A, Sohn H, et al. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect (Larchmt)* 2012;13(2):74-84. doi: 10.1089/sur.2011.058
11. Findlay JM, Kafsi JE, Hammer C, et al. Nonoperative Management of Appendicitis in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Coll Surg* 2016;223(6):814-24 e2. doi: 10.1016/j.jamcollsurg.2016.09.005
12. Salminen P, Paajanen H, Rautio T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA* 2015;313(23):2340-8. doi: 10.1001/jama.2015.6154
13. Ehlers AP, Talan DA, Moran GJ, et al. Evidence for an Antibiotics-First Strategy for Uncomplicated Appendicitis in Adults: A Systematic Review and Gap Analysis. *J Am Coll Surg* 2016;222(3):309-14. doi: 10.1016/j.jamcollsurg.2015.11.009
14. Anderson JE, Bickler SW, Chang DC, et al. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. *World J Surg* 2012;36(12):2787-94. doi: 10.1007/s00268-012-1749-z
15. Felson B. Appendical calculi; incidence and clinical significance. *Surgery* 1949;25(5):734-7.
16. Shindoh J, Niwa H, Kawai K, et al. Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. *J Gastrointest Surg* 2010;14(2):309-14. doi: 10.1007/s11605-009-1094-1

17. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg* 2015;50(11):1893-7. doi: 10.1016/j.jpedsurg.2015.07.008
18. Gaskill CE SV, Carnell J, Hippe DS, Bhargava P, Flum DR, Davidson GH. Use of Computed Tomography to Determine Perforation in Patients with Acute Appendicitis. *Current Problems in Diagnostic Radiology* 2016 doi: http://dx.doi.org/10.1067/j.cpradiol.2016.12.002 [published Online First: December 7, 2016]
19. O'Leary DP, Lynch N, Clancy C, et al. International, Expert-Based, Consensus Statement Regarding the Management of Acute Diverticulitis. *JAMA Surg* 2015;150(9):899-904. doi: 10.1001/jamasurg.2015.1675
20. Vennix S, Morton DG, Hahnloser D, et al. Systematic review of evidence and consensus on diverticulitis: an analysis of national and international guidelines. *Colorectal Dis* 2014;16(11):866-78. doi: 10.1111/codi.12659
21. Morris AM, Regenbogen SE, Hardiman KM, et al. Sigmoid diverticulitis: a systematic review. *JAMA* 2014;311(3):287-97. doi: 10.1001/jama.2013.282025
22. Talan DA SD, Mower WR, Krishnadasan A, Jude CM, Amii R, DeUgarte DA, Wu JX, Pathmarajah K, Morim A, Moran GJ, for the Olive View-UCLA Appendicitis Study Group. Antibiotics first versus surgery for appendicitis: A US pilot randomized controlled trial allowing outpatient antibiotic management. *Ann Emerg Med* 2016 doi: (doi:10.1016/j.annemergmed.2016.08.446)
23. Ehlers AP, Davidson GH, Bizzell BJ, et al. Engaging Stakeholders in Surgical Research: The Design of a Pragmatic Clinical Trial to Study Management of Acute Appendicitis. *JAMA Surg* 2016;151(6):580-2. doi: 10.1001/jamasurg.2015.5531
24. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010
25. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43.
26. Amtmann D, Cook KF, Johnson KL, et al. The PROMIS initiative: involvement of rehabilitation stakeholders in development and examples of applications in rehabilitation research. *Arch Phys Med Rehabil* 2011;92(10 Suppl):S12-9. doi: 10.1016/j.apmr.2011.04.025
27. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995;82(2):216-22.
28. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making* 2003;23(4):281-92.
29. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11(1):79-109. doi: 10.1089/sur.2009.9930
30. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):801-10. doi: 10.1001/jama.2016.0287
31. Le QA, Doctor JN, Zoellner LA, et al. Minimal clinically important differences for the EQ-5D and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized Preference Trial (DRPT). *Health Qual Life Outcomes* 2013;11:59. doi: 10.1186/1477-7525-11-59

32.Koumarelas K, Theodoropoulos GE, Spyropoulos BG, et al. A prospective longitudinal evaluation and affecting factors of health related quality of life after appendectomy. *Int J Surg* 2014;12(8):848-57. doi: 10.1016/j.ijsu.2014.06.015
33. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. *Stat Med* 1999;18(15):1905-42.
34. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308(24):2594-604. doi: 10.1001/jama.2012.87802
35. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309(8):814-22. doi: 10.1001/jama.2013.879
36. Turner L, Shamseer L, Altman DG, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev* 2012;11:MR000030. doi: 10.1002/14651858.MR000030.pub2
37. Angrist JD, Imbens GW. 2-Stage Least-Squares Estimation of Average Causal Effects in Models with Variable Treatment Intensity. *J Am Stat Assoc* 1995;90(430):431-42. doi: Doi 10.2307/2291054
38. Little RJ, Yau LHY. Statistical techniques for analyzing data from prevention trials: Treatment of no-shows using Rubin's causal model. *Psychol Methods* 1998;3(2):147-59. doi: Doi 10.1037/1082-989x.3.2.147
39. Bloom HS. Accounting for No-Shows in Experimental Evaluation Designs. *Evaluation Rev* 1984;8(2):225-46. doi: Doi 10.1177/0193841x8400800205
40. Diggle PJ HP, Liang KY, Zeger SL. Analysis of Longitudinal Data. Second Edition ed2002.
41. Turhan AN, Kapan S, Kutukcu E, et al. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2009;15(5):459-62.
42. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ* 2009;180(10):E47-57. doi: 10.1503/cmaj.090523
43. Khalil M, Rhee P, Jokar TO, et al. Antibiotics for appendicitis! Not so fast. *J Trauma Acute Care Surg* 2016;80(6):923-32. doi: 10.1097/TA.0000000000001030
44. Sitlani CM, Heagerty PJ, Blood EA, et al. Longitudinal structural mixed models for the analysis of surgical trials with noncompliance. *Stat Med* 2012;31(16):1738-60. doi: 10.1002/sim.4510
45. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. *JAMA* 2014;312(1):85-6. doi: 10.1001/jama.2014.7523

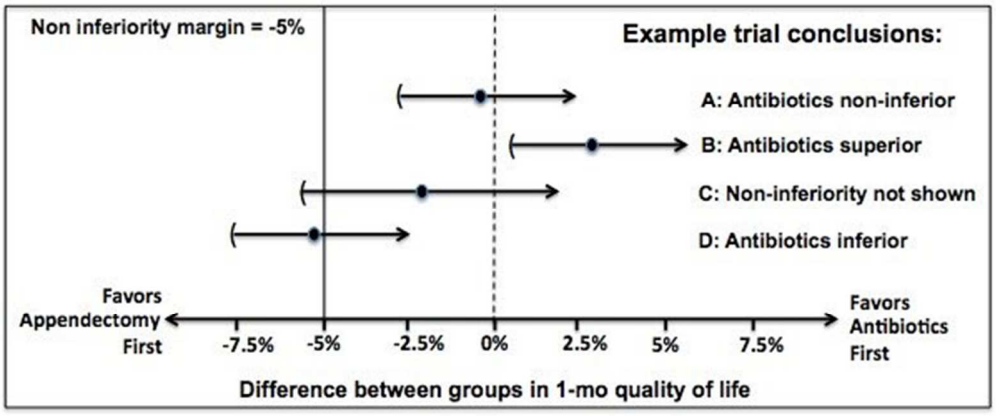

Figure 1

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SPIRIT
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)	

Introduction			
Background and rationale	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	
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	
Trial design	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)	
Methods: Participants, interventions, and outcomes			
Study setting	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	
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	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	
Participant timeline	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)	

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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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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.

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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

the treatment of choice for 120 years, the successful use of antibiotics was reported both in a series of over 500 patients treated with Strepotomycin 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 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 post-interventional complications (reported as clinical wound infections, incisional hernia, abdominal pain or obstructive symptoms) in the antibiotics group requiring intervention 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, no study used a validated patient-reported outcome (PRO) tool to measure the patient's experience in a standardized fashion. Other important outcomes to patients such as impact on work and school productivity, lingering symptoms, decisional regret, and healthcare burden (such as emergency room care or future imaging) were not included in prior studies. Furthermore, prior studies regimented care in ways that are not consistent with care in the United States (US), such as requiring several days of in-hospital convalescence. These limitations may explain the infrequent use of antibiotics as the primary treatment for appendicitis in the US.[14]

In addition to the need to address these limitations, there are additional, unresolved questions that make a larger, more definitive study of this treatment question important. First, there may be important subgroups of people with acute appendicitis who experience the treatment differentially. These might include older patients, who are at higher risk for surgical complications, those with possible appendiceal perforation detected on imaging, or those with an appendicolith. The association between appendicolith and worse outcomes with antibiotics is unclear. Appendicoliths are found in up to 20% of appendicitis cases; a similar proportion is also described in autopsy studies of normal appendices.[15] In several pediatric studies and at least one adult study, appendicolith seemed to be associated with eventual appendectomy; however, since

many trials did not include standardized imaging or criteria for requiring appendectomy following antibiotic therapy for appendicitis, it is unclear if the presence of an appendicolith actually confers a greater risk.[16 17] There is currently no standard definition of "complicated" disease. In the United States, usual care for appendiceal abscess or phegmon (inflammation so significant that surgeons are concerned for associated surgical morbidity) is antibiotics with consideration for interval appendectomy. Optimal treatment strategies for preoperative radiographic findings of appendiceal perforation is an area of controversy. The use of radiologic imaging to accurately determine perforation is limited; in prior randomized trials, patients with perforation were likely to have been inadvertently included due to a lack of imaging.[18] Finally, the European studies mandated the use of inpatient antibiotics at a time when there was a growing use of outpatient antibiotic regimens for similar conditions, such as acute diverticulitis.[19-21] A recently completed, pilot randomized trial in the US found that 14 of 15 adults randomized to antibiotics could successfully be discharged from the emergency department (ED) and receive all their care as outpatients, resolving their symptoms of acute appendicitis.[22] One of the remaining questions is whether this total outpatient approach to antibiotics would be as good as appendectomy in usual practice.

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

TRIAL DESIGN

Stakeholder Input in Design, Informed Consent, and Protocol

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

Because appendectomy was considered the standard and nearly universal therapy in the US, advisors recommended a study that considered the non-inferiority of the antibiotics-first strategy. As one advisor said, "the burden of proof is on the

antibiotics treatment approach to demonstrate that it is as good as appendectomy" (or not inferior by more than a small margin). Advisors also favored a non-inferiority framework because the larger size required for this design would also allow for multiple planned sub-group analyses for patient groups of interest and the possibility that superiority of the PRO measure might be demonstrated. Lastly, advisors suggested a parallel observational cohort to assess for potential selection bias for patients who declined randomization.

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

Study Aims and Hypothesis

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

Study population

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

Exclusion Criteria

- Inability to participate in follow-up (i.e., incarcerated, travel without access to phone, email)
- Contraindication to one of the study treatment arms:
    - Septic shock (evidence of severe sepsis or septic shock includes new presumed sepsis-related organ dysfunction, elevated lactate, and/or fluid unresponsive hypotension)
    - 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=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	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 antibiotics[29] 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[30], 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. In addition, 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 are collected and will be reported 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 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 delegate 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

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

The results from the European trials of antibiotics have not significantly changed care delivery in the US and have been met with resistance, in part due to the evidence gaps cited earlier and concern about the fate of patients with recurrent disease.[43] American patients may also have different expectations and resources that influence perception of treatment success and satisfaction with treatments. One particular protocol component of the European trials that may make them less applicable to the US

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.

References

1. Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132(5):910-25.
2. Chang DC, Shiozawa A, Nguyen LL, et al. Cost of inpatient care and its association with hospital competition. *J Am Coll Surg* 2011;212(1):12-9. doi: 10.1016/j.jamcollsurg.2010.09.014
3. Dieleman JL, Baral R, Birger M, et al. US Spending on Personal Health Care and Public Health, 1996-2013. *JAMA* 2016;316(24):2627-46. doi: 10.1001/jama.2016.16885
4. Coldrey E. Five years of conservative treatment of acute appendicitis. *J Int Coll Surg* 1959;32:255-61.
5. Wojciechowicz KH, Hoffkamp HJ, van Hulst RA. Conservative treatment of acute appendicitis: an overview. *Int Marit Health* 2010;62(4):265-72.
6. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 2006;30(6):1033-7. doi: 10.1007/s00268-005-0304-6
7. Hansson J, Korner U, Khorram-Manesh A, et al. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 2009;96(5):473-81. doi: 10.1002/bjs.6482
8. Eriksson S, Granstrom L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995;82(2):166-9.
9. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377(9777):1573-9. doi: 10.1016/S0140-6736(11)60410-8
10. Mason RJ, Moazzez A, Sohn H, et al. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect (Larchmt)* 2012;13(2):74-84. doi: 10.1089/sur.2011.058
11. Findlay JM, Kafsi JE, Hammer C, et al. Nonoperative Management of Appendicitis in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Coll Surg* 2016;223(6):814-24 e2. doi: 10.1016/j.jamcollsurg.2016.09.005
12. Salminen P, Paajanen H, Rautio T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA* 2015;313(23):2340-8. doi: 10.1001/jama.2015.6154
13. Ehlers AP, Talan DA, Moran GJ, et al. Evidence for an Antibiotics-First Strategy for Uncomplicated Appendicitis in Adults: A Systematic Review and Gap Analysis. *J Am Coll Surg* 2016;222(3):309-14. doi: 10.1016/j.jamcollsurg.2015.11.009
14. Anderson JE, Bickler SW, Chang DC, et al. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. *World J Surg* 2012;36(12):2787-94. doi: 10.1007/s00268-012-1749-z
15. Felson B. Appendical calculi; incidence and clinical significance. *Surgery* 1949;25(5):734-7.
16. Shindoh J, Niwa H, Kawai K, et al. Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. *J Gastrointest Surg* 2010;14(2):309-14. doi: 10.1007/s11605-009-1094-1

17. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg* 2015;50(11):1893-7. doi: 10.1016/j.jpedsurg.2015.07.008
18. Gaskill CE SV, Carnell J, Hippe DS, Bhargava P, Flum DR, Davidson GH. Use of Computed Tomography to Determine Perforation in Patients with Acute Appendicitis. *Current Problems in Diagnostic Radiology* 2016 doi: http://dx.doi.org/10.1067/j.cpradiol.2016.12.002 [published Online First: December 7, 2016]
19. O'Leary DP, Lynch N, Clancy C, et al. International, Expert-Based, Consensus Statement Regarding the Management of Acute Diverticulitis. *JAMA Surg* 2015;150(9):899-904. doi: 10.1001/jamasurg.2015.1675
20. Vennix S, Morton DG, Hahnloser D, et al. Systematic review of evidence and consensus on diverticulitis: an analysis of national and international guidelines. *Colorectal Dis* 2014;16(11):866-78. doi: 10.1111/codi.12659
21. Morris AM, Regenbogen SE, Hardiman KM, et al. Sigmoid diverticulitis: a systematic review. *JAMA* 2014;311(3):287-97. doi: 10.1001/jama.2013.282025
22. Talan DA SD, Mower WR, Krishnadasan A, Jude CM, Amii R, DeUgarte DA, Wu JX, Pathmarajah K, Morim A, Moran GJ, for the Olive View-UCLA Appendicitis Study Group. Antibiotics first versus surgery for appendicitis: A US pilot randomized controlled trial allowing outpatient antibiotic management. *Ann Emerg Med* 2016 doi: (doi:10.1016/j.annemergmed.2016.08.446)
23. Ehlers AP, Davidson GH, Bizzell BJ, et al. Engaging Stakeholders in Surgical Research: The Design of a Pragmatic Clinical Trial to Study Management of Acute Appendicitis. *JAMA Surg* 2016;151(6):580-2. doi: 10.1001/jamasurg.2015.5531
24. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010
25. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43.
26. Amtmann D, Cook KF, Johnson KL, et al. The PROMIS initiative: involvement of rehabilitation stakeholders in development and examples of applications in rehabilitation research. *Arch Phys Med Rehabil* 2011;92(10 Suppl):S12-9. doi: 10.1016/j.apmr.2011.04.025
27. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995;82(2):216-22.
28. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making* 2003;23(4):281-92.
29. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11(1):79-109. doi: 10.1089/sur.2009.9930
30. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):801-10. doi: 10.1001/jama.2016.0287
31. Le QA, Doctor JN, Zoellner LA, et al. Minimal clinically important differences for the EQ-5D and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized Preference Trial (DRPT). *Health Qual Life Outcomes* 2013;11:59. doi: 10.1186/1477-7525-11-59

32.Koumarelas K, Theodoropoulos GE, Spyropoulos BG, et al. A prospective longitudinal evaluation and affecting factors of health related quality of life after appendectomy. *Int J Surg* 2014;12(8):848-57. doi: 10.1016/j.ijsu.2014.06.015
33. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. *Stat Med* 1999;18(15):1905-42.
34. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308(24):2594-604. doi: 10.1001/jama.2012.87802
35. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309(8):814-22. doi: 10.1001/jama.2013.879
36. Turner L, Shamseer L, Altman DG, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev* 2012;11:MR000030. doi: 10.1002/14651858.MR000030.pub2
37. Angrist JD, Imbens GW. 2-Stage Least-Squares Estimation of Average Causal Effects in Models with Variable Treatment Intensity. *J Am Stat Assoc* 1995;90(430):431-42. doi: Doi 10.2307/2291054
38. Little RJ, Yau LHY. Statistical techniques for analyzing data from prevention trials: Treatment of no-shows using Rubin's causal model. *Psychol Methods* 1998;3(2):147-59. doi: Doi 10.1037/1082-989x.3.2.147
39. Bloom HS. Accounting for No-Shows in Experimental Evaluation Designs. *Evaluation Rev* 1984;8(2):225-46. doi: Doi 10.1177/0193841x8400800205
40. Diggle PJ HP, Liang KY, Zeger SL. Analysis of Longitudinal Data. Second Edition ed2002.
41. Turhan AN, Kapan S, Kutukcu E, et al. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2009;15(5):459-62.
42. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ* 2009;180(10):E47-57. doi: 10.1503/cmaj.090523
43. Khalil M, Rhee P, Jokar TO, et al. Antibiotics for appendicitis! Not so fast. *J Trauma Acute Care Surg* 2016;80(6):923-32. doi: 10.1097/TA.0000000000001030
44. Sitlani CM, Heagerty PJ, Blood EA, et al. Longitudinal structural mixed models for the analysis of surgical trials with noncompliance. *Stat Med* 2012;31(16):1738-60. doi: 10.1002/sim.4510
45. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. *JAMA* 2014;312(1):85-6. doi: 10.1001/jama.2014.7523

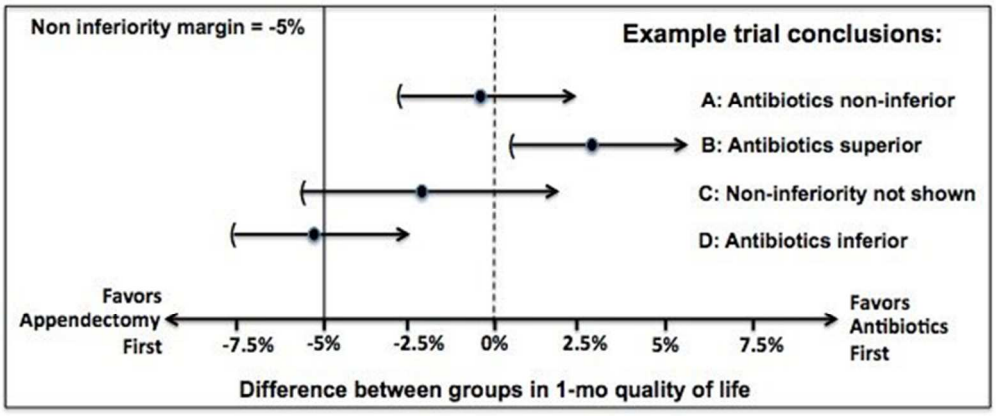

Figure 1

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SPIRIT
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)	

Introduction			
Background and rationale	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	
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	
Trial design	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)	
Methods: Participants, interventions, and outcomes			
Study setting	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	
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	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	
Participant timeline	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)	

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.