Antibiotic Instillation in Acute Complex Appendicitis for Prevention of Deep Space Surgical Site Infections

Antibiotic Instillation in Appendicitis

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EXPERIMENTAL SCHEMA

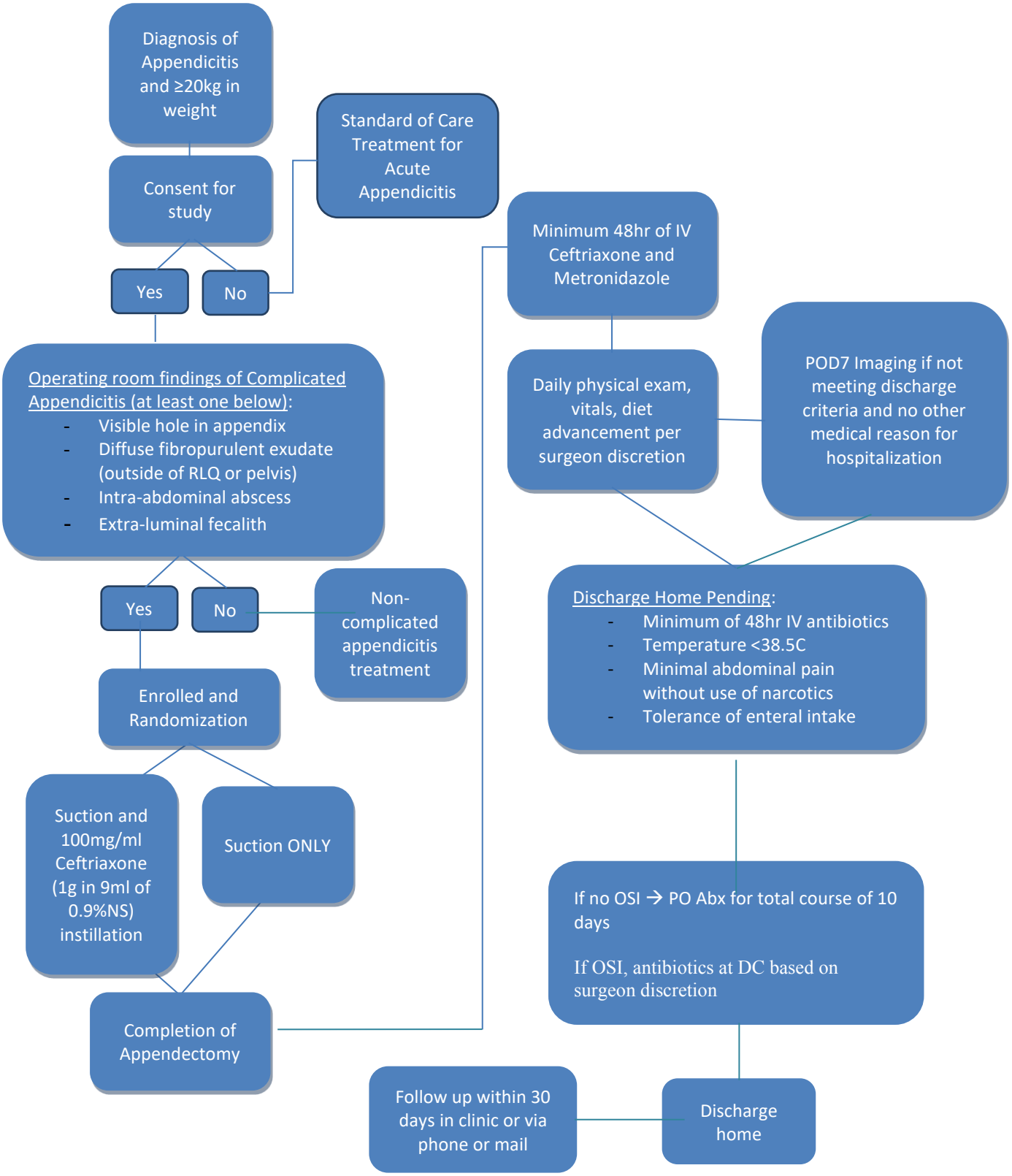
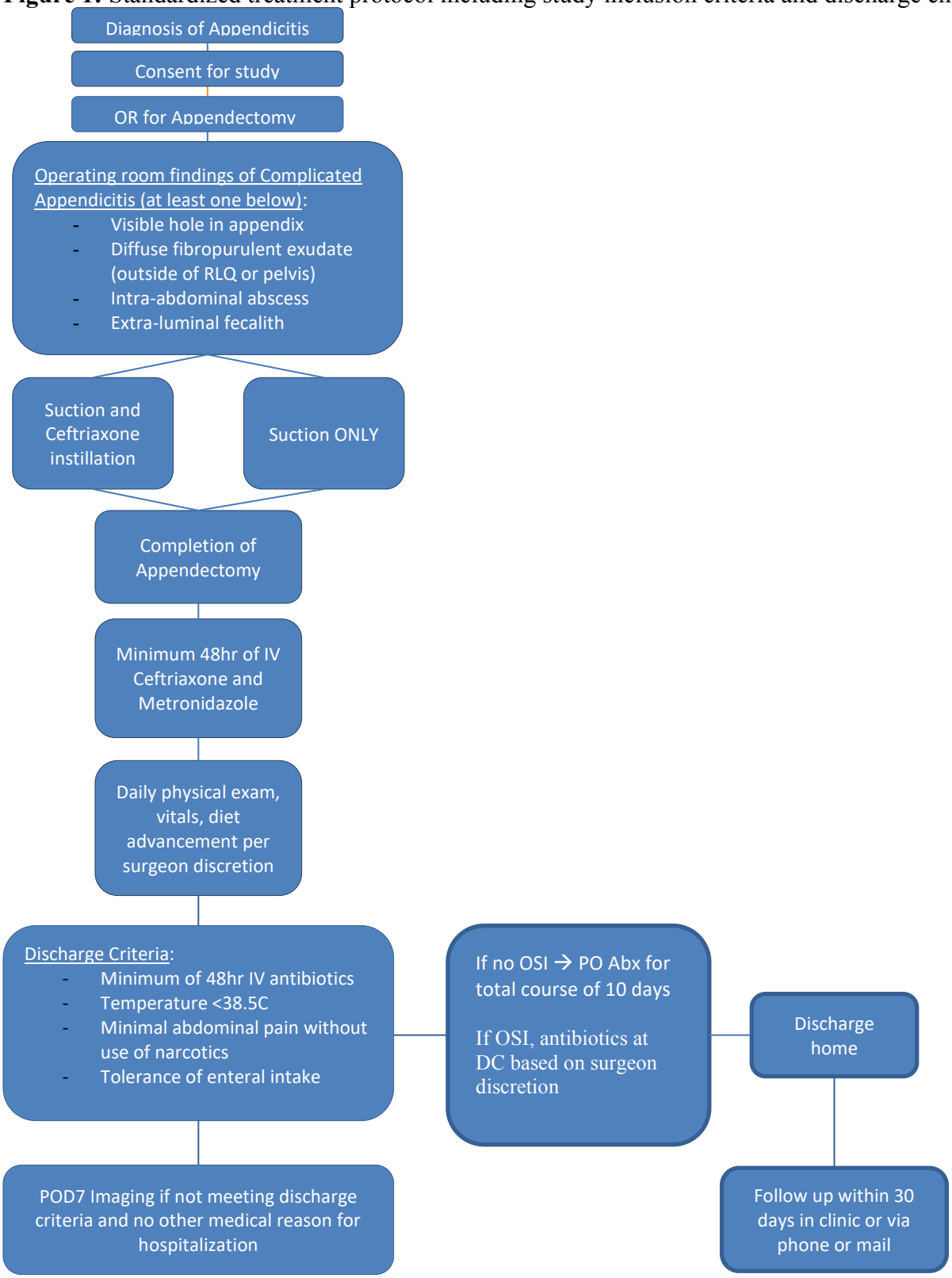


Figure 1: Standardized treatment protocol including study inclusion criteria and discharge checklist.



PROTOCOL SIGNATURE

I confirm that I have read and understood this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

_____ _____

Signature of Principal Investigator **Date**

Nicole Chandler, MD

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Principal Investigator Name (Print)

Johns Hopkins All Children's Hospital

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Name of Institution

STUDY SUMMARY

Title	Antibiotic Instillation in Acute Complex Appendicitis for Prevention of Deep Space Surgical Site Infections
Short Title	Antibiotic Instillation in Appendicitis
IND	IND
Phase	Pilot Phase 2
Design	Randomized single blind control study
Study Duration	1 year
Study Center(s)	Single-center
Objectives	The primary objective is to evaluate the feasibility and safety of the use of antibiotic instillation in the treatment of complex acute appendicitis measured by enrollment rates and ability to complete all study tasks. Secondary objectives are to examine the rate of intra-abdominal abscess formation and post-operative length of stay following treatment of complex appendicitis in the setting of appendectomy with intra-operative suction alone compared to suction with intra-peritoneal antibiotic instillation
Number of Participants	A total of 36 patients will be randomized to two groups in this pilot study
Diagnosis and Main Eligibility Criteria	Intraoperative diagnosis of complex appendicitis defined by: a visible hole in the appendix, extra-luminal fecalith, diffuse fibropurulent exudate (outside the right lower quadrant (RLQ)/pelvis) or presence of intra-peritoneal abscess
Study Product, Dose, Route, Regimen	Ceftriaxone, >20kg (1g in 9ml of 0.9% normal saline), intraperitoneal instillation given once following appendectomy, and aspiration of excess intra-peritoneal fluid
Duration of Administration	A one-time dose of intra-peritoneal ceftriaxone solution following appendectomy
Reference Therapy	Standard of care is intra-peritoneal aspiration alone, or irrigation of the peritoneal cavity with or without antibiotic in the irrigant fluid.
Statistical Methodology	Descriptive statistics will be used to summarize the results. Continuous variables will be summarized using means and standard deviation or median and range as appropriate. Categorical variables will be summarized using counts and percentages. Data will be presented using tables and figures

1 OBJECTIVES

1.1.1 Primary objective

To evaluate the feasibility and safety of the use of antibiotic solution instillation following intraoperative diagnosis of complex appendicitis. We will determine feasibility by the percentage of eligible participants who (1) agree to participate, and (2) complete all intervention sessions and measurement time points. Safety will be evaluated by adverse events associated with the use of intra-peritoneal antibiotic instillation for the treatment of peritonitis caused by complex appendicitis.

1.1.2 Secondary objectives

A. To evaluate preliminary efficacy of antibiotic solution instillation following diagnosis of complex appendicitis.

B. To compare the following outcomes between patients who receive or do not receive antibiotic solution instillation following diagnosis of complicated appendicitis: operative time, length of stay, post-operative antibiotic use, post-operative pain medication use, need for post-operative imaging, readmission rates, and the development of intra-peritoneal abscess requiring percutaneous aspiration and/or drainage within 30-days following appendectomy.

2 BACKGROUND AND RATIONALE

Appendicitis is the most common abdominal surgical emergency in children, affecting approximately 75,000 children a year.[1, 2] Mitigating the associated morbidities of this disease process is of paramount concern to the pediatric surgeon.[1] In complicated or complex appendicitis, the infectious process is noted to have progressed beyond the confines of the appendix, which leads to purulent fluid in the intra-peritoneal space (diffuse exudate outside of the right lower quadrant (RLQ)/pelvis), a visible hole (perforation) of the appendix, an extra-luminal fecalith, or an intra-peritoneal abscess. Complex appendicitis occurs in up to 20% of all cases of appendicitis and is associated with a much higher morbidity and mortality than its simple counterpart.[1, 3-5]

The ensuing systemic response from complex appendicitis has a significant impact on the patient and their families. Complex appendicitis results in significant morbidity, with increased rates of intra-peritoneal abscess formation, and surgical site infections, as well as increased length of stay. [6, 7] The increased inflammation and bacterial insult can result in urinary retention, diarrhea, increased pain, and a high incidence of deep organ space infection. [6] In the peritoneal space, infection can progress to form an intra-abdominal abscess, which is treated with intravenous antibiotics and often percutaneous or operative drainage. All of these factors in combination with the increased level of systemic insult experienced by the patient, correlate with longer and more costly hospital stays, increased need for advanced imaging leading to more radiation exposure, prolonged antibiotic use, and increased discomfort and generalized malaise, more time away from school, work, and home.

Current management strategies for intra-operatively diagnosed complex appendicitis include appendectomy with aspiration of infected intra-peritoneal fluid followed by continued post-operative treatment with intravenous or oral antibiotic therapy.[8] Previous studies have not seen dramatic

improvements with antibiotic irrigation, large volume irrigation, or prophylactic intra-peritoneal drain use to prevent intra-abdominal abscess formation.[9-18] As such, the search continues to find an answer to the high rate of deep space infection associated with complex appendicitis, which can be as high as 45%.[5, 19]

Interventions to counter these negative effects currently focus on the aftermath of an intra-abdominal abscess and how to manage it once it has been identified. Previous studies have investigated the use of peritoneal irrigation solutions (with or without antibiotics) at the time of surgery, in hopes of decreasing intra-abdominal abscess rates and length of stay following appendectomy, but these studies did not show any significant improvement in abscess rates after irrigation compared to aspiration alone.[5, 18, 20] These previous studies may not have observed an improvement in post-operative complications given that they did not allow for the antibiotic solution to remain in the intraperitoneal space.

The current pilot project focuses on assessing the feasibility of using antibiotic instillation to prevent deep organ space surgical site infection, which would be a significant improvement to the existing standard of care. Currently there is no literature that describes utilizing antibiotic instillation in the treatment of complicated appendicitis, thus this pilot study will provide important feasibility data prior to instituting a large multicenter trial. Pending feasibility of our pilot study, our project will further study the length of stay, and potential prevention of intra-abdominal abscess. The outcomes of this limited efficacy testing will be an important initial step to designing a larger, multicenter trial which is powered to show improved postoperative outcomes with decreased postoperative abscess formation in complicated appendicitis.

We believe that after appendectomy and removal of the nidus of disease, the post-operative field would benefit from treatment with an antibiotic instillation, a solution placed in the peritoneal cavity in direct contact with the contaminated surfaces. By leaving the antibiotic solution in place at time of closure, the contaminated areas are topically treated with prolonged exposure to the bactericidal effects of ceftriaxone (). This technique will give appropriate temporal contact of the medication to the bacteria, allowing for better dispersion, and optimized efficacy.

In patients with peritoneal dialysis catheters, infection of these catheters can lead to peritonitis, or inflammation of the peritoneal cavity, which, in turn can progress to sepsis. Peritonitis associated with infected peritoneal dialysis catheters is treated with antibiotic instillation into the peritoneal cavity with demonstrated success and is currently considered the standard of care treatment.[21-24] Intra-peritoneal antibiotic instillation is the current standard of care for treatment of peritonitis associated with PD catheters.[25] Given that intra-peritoneal antibiotic instillation is the standard of care for PD catheter associated peritonitis, it should also be safe to use for any type of peritonitis, and in this case, peritonitis due to complicated appendicitis.

Recently, the treatment regimens have shifted away from continuous use of antibiotic instillations during PD sessions and have moved towards intermittent antibiotic instillations with daily dosing.[26, 27] The International Society for Peritoneal Dialysis (ISPD) recommends at least a 6 hour dwell time for intermittent antibiotic instillation to allow for adequate absorption.[25] The ISPD guidelines also suggest that cephalosporins be administered on a daily intermittent basis, or continuously (with each exchange), as there is no significant difference in peritonitis treatment outcomes with these dosing regimens.[25] Given the broad coverage, we believe that the intra-peritoneal use of ceftriaxone will lead to better treatment of complex appendicitis and potentially decreased incidence of intra-abdominal abscesses. This aligns with typical treatment strategies for peritonitis associated with PD catheters, which have been successful.[22, 26, 28] Second or third generation cephalosporins are the standard of care antibiotics used pre-operatively prior to an appendectomy. At our institution pre-operative intravenous (IV) ceftriaxone (50mg/kg/day,

maximum 2g daily) and metronidazole (30mg/kg/day) therapy is used as pre-operative antibiotic treatment prior to pediatric appendectomy. [29] Intravenous ceftriaxone (50mg/kg/day, maximum 2g daily) and metronidazole(30mg/kg/day) is given post-operatively following the diagnosis of complicated appendicitis for a minimum of 48 hours following surgery. The maximum daily dosage of intravenous ceftriaxone administered during the conduct of the study will be 2g. We anticipate that the intra-peritoneal instillation of ceftriaxone will decrease the length of stay and decrease the post-operative development of deep organ space surgical site infection in patients with complicated appendicitis due to the longer contact with the inflamed area of the RLQ following removal of the nidus of infection, or the appendix. A small volume of instilled ceftriaxone (~10ml solution total) will be used so as not to instill a significant amount of additional fluid into the peritoneal cavity.

The idea of surgical source control paired with direct antibiotic instillation and application to the area of infection is an innovative approach to the traditional treatment scheme of complicated appendicitis which could be instrumental in decreasing post-operative complications. Antibiotic instillation into the peritoneal cavity after appendectomy gives maximal contact time between the antibiotic and the bacteria in question, and leads to elevated local antibiotic concentration. To our knowledge, no study has ever sought to use antibiotics as a topical, retained solution in an infected peritoneum due to complicated appendicitis. We believe that by applying the antibiotics directly to site of highest bacterial presence and allowing the medication to remain in contact with this field, that the overall response will be better bacterial control and decreased rates of intra-abdominal abscess formation and complications. This is a new concept and has not yet been reported in pediatric patients with complicated appendicitis. The long-term goal of the study is to compare incidence of postoperative deep organ space infection following our standard of care (aspiration of intra-peritoneal infected fluid only) compared with aspiration of intra-peritoneal infected fluid followed by antibiotic instillation of ceftriaxone. This pilot study will evaluate the feasibility of this novel approach and will yield the necessary preliminary data for a larger study to evaluate the effectiveness of this treatment scheme.

2.1 **Benefit / Risk Assessment**

Appendicitis is one of the most common surgical diagnoses in the pediatric population and the most common surgical emergency in children.[1, 2] In complex appendicitis, the sequelae have progressed beyond the confines of the organ, and have led to purulent fluid in the intra-abdominal space, spillage of intestinal contents, or gross perforation of the appendix. Complicated appendicitis occurs in up to 20% of cases and is associated with a much higher morbidity and mortality. [5] Previous studies have shown that local treatment of peritonitis associated with PD catheters with intra-peritoneal antibiotics has had significant improvement of outcomes.[22, 23, 26, 28] The intra-peritoneal route is preferable as compared to oral and intravenous antibiotic administration due to elevated local levels of the antibiotic above the minimum inhibitory concentration while avoiding venipuncture and systemic side effects.[25, 26] There is minimal risk associated with involvement in this study given that we will be screening for any history of allergies to penicillin or cephalosporins, and excluding these patients. Ceftriaxone is commercially available, has a low risk profile, and is generally well tolerated with minimal side effects.

Our treatment period will include a one-time intra-operative dose of intra-peritoneal ceftriaxone. Typical dosing strategies for intra-peritoneal ceftriaxone administration occur on a daily basis, so our treatment period will also include the 24 hours following intra-peritoneal administration of ceftriaxone. All patients diagnosed with acute complicated appendicitis intra-operatively, and entered into our study, will also receive a minimum 48 hours of intravenous antibiotics as an inpatient, allowing for continued observation. We will be treating pediatric patients who are intra-

operatively diagnosed with complex appendicitis, as defined by any of the following: visible hole in the appendix, extra-luminal fecalith, diffuse fibropurulent exudate outside the RLQ/pelvis, or intraperitoneal abscess. All patients will have been admitted to Johns Hopkins All Children's Hospital with a diagnosis of acute appendicitis prior to surgical intervention. Patients will then be randomized once diagnosed with complex appendicitis intra-operatively. Patients with allergies to penicillin or cephalosporins will be excluded pre-operatively, as well as patients who do not meet the weight requirement, are pregnant, have a history of neurological conditions such as encephalopathy, seizures, myoclonus and non-convulsive status epilepticus, have a known inability to complete a 30day postoperative follow up, are being treated non-operatively, and those who have been intra-operatively diagnosed with simple appendicitis.

3 DRUG INFORMATION

Ceftriaxone is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous, intramuscular, or intra-peritoneal administration.

Ceftriaxone sodium is (6*R*,7*R*)-7-[2-(2Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7[2]-(*Z*)(*O*-methyloxime), disodium salt, sesquaterhydrate. The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$.

Ceftriaxone is a white powder, which is soluble in water. In this study ceftriaxone crystalline powder will be dissolved in 0.9% sodium chloride solution prior to intra-peritoneal instillation.

1g of ceftriaxone will dissolve in 9ml of 0.9% of sodium chloride solution, and when fully withdrawn should result in a total volume of just about 10ml (9.8ml) for intra-peritoneal instillation.

4 STUDY DESIGN

This is a Prospective Randomized Open with Blinding of Endpoint (PROBE) pilot phase 2 study to evaluate the feasibility and safety of the use of antibiotic instillation in the treatment of complex acute appendicitis. All children equal to or greater than 20kg diagnosed with acute appendicitis and undergoing urgent appendectomy will be approached for enrollment for this study. As there is poor pre-operative diagnostic accuracy for simple versus complex appendicitis, all eligible patients presenting with acute appendicitis and their families will be approached for consent. Intra-operative assessment will diagnose complex appendicitis. Complex appendicitis will be defined as presence of any of the following: visible hole in the appendix, extra-luminal fecalith, diffuse fibropurulent exudate outside the right lower quadrant (RLQ)/pelvis, or intraperitoneal abscess. Patients will be excluded if they undergo non-operative management of appendicitis, do not undergo appendectomy at the time of operation, weigh less than 20kg, are pregnant, are unable to complete a 30day postoperative follow up, have impaired renal function (CrCl <15mL/min), have a history of neurological conditions (such as encephalopathy, seizures, myoclonus, and non-convulsive status epilepticus), or are allergic to penicillin or cephalosporins that prohibit the use of the antibiotic intra-peritoneal instillation. Patients with a history of anaphylactic reactions to penicillin or cephalosporins will be excluded from this study. Patients with a penicillin allergy who have previously received IV cephalosporins without allergic reaction will be considered for inclusion in this study.

Study participants will be randomized in a 1:1 ratio using permuted blocks of 4 and 6 using a computer-generated randomization scheme. The treatment category assignments will be placed in consecutive numbered envelopes concealed from study staff until randomization. In the operating room, once the patient is diagnosed with complicated appendicitis, then the next sequential envelope will be opened and the patient will be assigned to that treatment arm. The surgeon and team administering the treatment will not be blinded; however, patients, their families, and hospital caregivers outside of the operating room will be blinded to the treatment. Post-operative protocols will be the same for both groups and includes continuation of intravenous antibiotics (Study Schema, and Fig 1). Once complex appendicitis is diagnosed, and a successful appendectomy occurs, then the patient will be transitioned to intravenous ceftriaxone (50mg/kg/day, maximum 2g daily) and metronidazole (30mg/kg/day) post-operatively. Both study groups will receive a minimum additional 48 hours of intravenous ceftriaxone and metronidazole, as per our weight based current standard of care. Patient status and post-operative recovery back to baseline will dictate discharge or continued hospitalization. Pending their clinical course, patients will be either transitioned to broad-spectrum oral antibiotics or continued on intravenous ceftriaxone and metronidazole until their discharge from the hospital. Our standardized discharge criteria includes: temperature less than 38.5ºC for the previous 24 hours, improved abdominal pain without the use of narcotics, and tolerance of enteral intake. Once these criteria have been met, and at the surgeon's discretion, the patient will be discharged home with routine follow-up (either a clinic visit, telemedicine visit, or a phone call) within 30 days after surgery.

If the patient remains hospitalized on post-operative day 7 (plus or minus 1 day) related to postoperative care of complicated appendicitis, and does not meet discharge criteria as listed, then they will undergo subsequent imaging studies (abdominal ultrasound or CT abdomen-pelvis) to evaluate for intra-abdominal abscess or phlegmon. If patients are found to have an abscess or phlegmon, they will continue to receive ongoing antibiotic treatment with or without percutaneous aspiration and/or drainage at the discretion of the surgeon and interventional radiologist.

Patients will undergo telephone, telemedicine visit, or in-person clinic follow-up within 30-days of their discharge following their appendectomy. If patients present with symptoms at these checks or independently present to an emergency department, they will undergo routine evaluation and imaging as clinically indicated. Other parameters that will be tracked include development of superficial or deep surgical site infection, inpatient pain scores, inpatient pain medication use, and post-operative length of stay.

An independent clinical endpoint committee will be formed to evaluate for study related complications and endpoints. For consistency and future ease of a prospective multicenter trial, definitions of intraoperative findings of complicated appendicitis, postoperative percutaneous drainage or aspiration of intraperitoneal fluid collection, surgical site infection, postoperative sepsis, readmission and/or reoperation will be reported according to the National Surgical Quality Improvement Program Pediatric Operations Manual, January 2022 edition. [31]

We will evaluate patient retention and recruitment along with the process of instilling antibiotic solution into the intra-peritoneal space in this feasibility study. We will primarily focus on recruitment, enrollment, and retention rates in this pilot study. We will also evaluate patient outcomes associated with intra-peritoneal instillation of antibiotics to determine not only post-operative complication rates, but also length of stay, pain scores, pain medication use, superficial surgical site infections, and adverse events related to the antibiotic instillation. Patients and their families will be blinded to their randomized treatment groups, and will be followed for 30 days following appendectomy.

4.1 Number of Participants

Thirty-six patients will be enrolled. We will screen approximately 400 patients within the eighteen-month period.

4.2 Number of Study Centers

This will be a single-center trial. Johns Hopkins All Children's Hospital will be the only participating hospital in this study.

4.3 Study Duration

We will begin screening patients after IRB approval of our pilot study. We will continue screening and inclusion in the trial until enrollment is met. We suspect this will take approximately eighteen months. The duration of participation will be approximately 30-days from the time of appendectomy. We will continue our pilot study until we have enrolled a total of 36 patients.

5 ELIGIBILITY CRITERIA

All children weighing equal to or greater than 20kg admitted to our institution with a diagnosis of acute appendicitis and who undergo urgent appendectomy will be eligible for this study. Patient and guardians will be approached with information about the study regardless of pre-operative categorization of appendicitis, suspected simple or suspected complex. The patient and family will be blinded as to which treatment arm they will receive.

5.1 Inclusion Criteria

5.1.1 Patient diagnosed with acute appendicitis and are scheduled to undergo urgent appendectomy

5.1.2 Patient is between 3-18 years of age at time of appendectomy

5.1.3 Patient has intraoperative findings of complex appendicitis defined by: visible hole in the appendix, extra-luminal fecalith, diffuse fibropurulent exudate outside the RLQ/pelvis, or intraperitoneal abscess

5.1.4 Patient weighs equal to or greater than 20kg at time of surgery

5.2 Exclusion Criteria

5.2.1 Patient is pregnant

5.2.2 Patient has a penicillin or cephalosporin allergy that is severe or anaphylactic in nature, prohibiting the use of these antibiotics

5.2.3 Patient has simple appendicitis

5.2.4 Patient who undergoes appendectomy following failed or planned medical management of appendicitis

5.2.5 Patient has impaired renal function (CrCl <15mL/min)

5.2.6 Patient has history of neurological conditions such as encephalopathy, seizures, myoclonus and non-convulsive status epilepticus

5.2.7 Patient has a known inability to complete a 30day postoperative follow up

6 ENROLLMENT GUIDELINES

Participants must meet all of the eligibility requirements listed in Section 5 prior to signing the IRB-approved informed consent form.

6.1 Screen Failures

Screen failures are defined as participants who consent to participate in the research but who are not subsequently randomized. Individuals who do not meet the criteria for participation in this study (screen fail) may not be re-screened.

7 ANTIBIOTIC INSTILLATION INTERVENTION PLAN

7.1 Intervention Schedule

All patients equal to or greater than 20kg presenting to Johns Hopkins All Children's Hospital with a diagnosis of acute appendicitis and are scheduled to undergo urgent appendectomy will be approached for participation in this study. Intra-operatively their eligibility to participate in the study will be determined. If complex appendicitis is found intra-operatively then the patient will be randomized into the control group (standard of care arm with intra-peritoneal fluid aspiration only), or the study group (intra-peritoneal fluid aspiration and antibiotic solution instillation). Antibiotic instillation will be introduced into the RLQ/pelvis after the appendectomy is completed and all intra-peritoneal fluid is aspirated. Ceftriaxone solution will be used depending on availability and pharmacy stock for use at Johns Hopkins All Children's Hospital. The ceftriaxone powder (1g) will be dissolved in 9ml of sterile normal saline. The entire contents of reconstituted powder will be fully withdrawn for a total instillation volume of 10ml. This fluid will then be instilled and left to dwell in the area of the peritoneal cavity where the appendix was removed.

Intervention

Standard of Care (Control group)/ARM A
Intra-operative aspiration of intra-peritoneal fluid after successful appendectomy.

Standard of Care and Antibiotic instillation (Study group)/ARM B
Intra-operative aspiration of intra-peritoneal fluid after successful appendectomy and subsequent instillation of 10ml of intra-peritoneal ceftriaxone (1g)

7.2 Third Generation Cephalosporin Intra-peritoneal Instillation Treatment

7.2.1 How Supplied, Stored, Packaged and Labeled

Ceftriaxone powder is stored in glass bottles in the OR Pyxis at room temperature with printed labels, noting dose and amount.

7.2.2 Preparation and Administration

The sterile ceftriaxone powder (1g) will be mixed with 9ml of sterile 0.9% normal saline. The entire contents of reconstituted powder will be fully withdrawn, for a total volume of 10mL. This solution will then be sterilely transferred to the surgical field and administered into the intra-peritoneal space under direct visualization prior to closure of the fascia.

7.2.3 Accountability and Compliance

Pending inclusion and randomization into the trial, the patient will be randomized into one of the two treatment arms. The patient will either receive the standard of care treatment arm, or the standard of care treatment arm with intra-peritoneal instillation of ceftriaxone. The amount of ceftriaxone used will be recorded in the patient's record in the EMR (Epic) by the circulating nurse in the operating room. The dose of ceftriaxone, and route will be verbally communicated to the operating surgeon who will agree with said treatment and document within their operative note.

7.3 Prohibited Concomitant Medications

Not applicable.

7.4 Duration of Therapy / Intervention

Participants must be withdrawn from the study treatment for the following reasons:

- Participant withdraws consent from the study treatment and/or study procedures. A participant must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a participant may decline to participate further. The participant will not suffer any disadvantage as a result.
- Participant is lost to follow-up.

- Death.

Participants may be withdrawn from the study for the following reasons:

- The participant is non-compliant with study drug, trial procedures, or both.
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Development of a concurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.

7.5 Lost to Follow Up

A participant will be considered lost to follow up if s/he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant. Where possible, three (3) telephone calls and a certified letter to the participant's last known mailing address per their medical record. These contact attempts will be documented in the research record.

8 TOXICITIES AND DOSE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) version 5.0 for adverse events and serious adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

8.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the **study intervention** even if the event is not considered to be related to study intervention. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study intervention. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

AEs will be collected from the date of the operative intervention (with or without instillation of antibiotics) to 30 days after the operative date. Given the one-time study intervention and dosing timeline, any adverse effects should be seen well within the first 48 hours after administration. However, we will continue to review, document, and intervene on any adverse events that occur within the first 30 days following surgery.

Information about adverse events, whether volunteered by the participant, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the participant at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine at a minimum:

1. The severity grade based on CTCAE v.5 (grade 1-5)
2. Its relationship to the study intervention (definite, probable, possible, unlikely, unrelated)
3. Its duration (start and end dates or if continuing at final exam)
4. Whether it constitutes an SAE

All adverse events are expected to be treated appropriately. Once an adverse event is detected, it will be followed until its resolution.

Information about common side effects already known about the commercial drug (third generation cephalosporin) is described in the Drug Information (section 3) and the FDA-approved product labels. This information is included in the participant informed consent and/or assent and will be discussed with the participant during the study, as needed.

All adverse events are recorded in the participant research chart.

8.2 Serious Adverse Events (SAEs)

Information about all serious adverse events is collected and recorded. A serious adverse event is one which meets any of the following criteria:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, (such as ongoing pain, fever, constipation, bowel obstruction, surgical site infections, or other infections)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the participant's general condition
    - Is medically significant (i.e. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above)

Events that fall within the definitions listed above must be reported as SAEs, irrespective of whether they are judged to be related to treatment or not. If an event is not an AE per the definition in section 9.1, then it cannot be an SAE, even if serious conditions are met (e.g. hospitalization, death due to progression of disease etc.). However, such events may meet JHM IRB reportable definitions as a UPIRSO (see section 9.3). Toxicities unrelated to treatment that

do NOT fall within the definitions above, must simply be documented as AEs in the participant research chart.

Collection of serious adverse events will begin after the patient is randomized into the study intra-operatively and will end 48 hours after administration of the intra-peritoneal antibiotics. It is very unlikely that any serious adverse event will occur given that this study intervention uses a commercially available antibiotic that is routinely administered both parenterally and locally. Adverse events due to intra-peritoneal antibiotic instillation may be difficult to distinguish given that similar antibiotics will be given intravenously.

8.3 Unanticipated Problems Involving Risks to Participants or Others (UPIRPO)

JHM IRB defines UPIRPOs as events or information that is unexpected in terms of nature, severity, or frequency given the research procedures described in the protocol, the informed consent form, and the characteristics of the participant populations AND indicates that participants or others are at greater risk of harm (physical, psychological, economic, or social) than previously known or recognized. Events meeting the JHM IRB requirements for UPIRPOs (https://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/103_6b.html) are reported promptly to JHM IRB.

8.4 Reporting Requirements

SAEs will be reported to the overall PI, and the IRB.

SAE and UPIRSO Reporting to the IRB:

- Events meeting the JHM IRB requirements for UPIRSOs will be reported promptly to the IRB.

The MedWatch report will be submitted to the FDA through the voluntary reporting method by the PI.

A MedWatch 3500A form must be completed and submitted to the FDA as soon as possible, but no later than 10 days of first knowledge or notification of event (5 days for fatal or life-threatening event).

MedWatch 3500A form can be found at:
https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting

8.5 Supportive Care

8.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

9 STUDY CALENDAR

MONTHLY Calendar

Test / Procedure	Pre-study[1]	Surgery	POD 1	POD 3	POD 4	POD 5	POD 6	POD 7	POD 14	POD <30
Informed consent	X									
Medical history	X									
Eligibility criteria	X									
Vital signs[2]	X		X	X	X	X	X	X	X	
Physical examination[2]	X		X	X	X	X	X	X	X	
CBC with diff[2]	X			X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Urine pregnancy test[4]	X									
Pain Score[2]	X	X	X	X	X	X	X	X	X	X
Randomization and record of treatment group		X								
Telephone or In-person Follow up									X	X
Pre-operative imaging (US or CT scan)	X									
Post-operative imaging (US or CT Scan)[5]								X[3]		

1 All Pre-study/Screening procedures should be completed within 24 hours of study enrollment
2 To occur if the patient is still admitted, or seen in follow up
3 To occur at the discretion of the surgeon when clinically warranted
4 Required for any female greater than 10 years old prior to receiving general anesthesia
5 If patient continues to have an elevated WBC, pain on exam, a fever within the last 24 hours or is unable to tolerate a diet.

10 STUDY PROCEDURES

Screening:

Informed Consent
Pre-op Physical exam: Height, weight, abdominal exam
Review of medical history/baseline symptoms including pain score
Pre-op Vitals: heart rate, blood pressure, respiratory rate, pulse oximetry, temperature
Pre-op pain score
Pre-op Labs: CBC w/diff, pregnancy test if warranted
Pre-op imaging: Ultrasound or CT scan

Surgery:

Successful appendectomy will be defined as removal of the appendix and appropriate closure of the cecum.
After successful appendectomy and identification of complex appendicitis, the patient will be randomized into the standard of care arm, or the standard of care with antibiotic instillation arm.

Post-operative monitoring:
Post-operative inpatient Physical exam: abdominal exam
Post-operative inpatient Vitals: heart rate, blood pressure, respiratory rate, pulse oximetry, temperature
Post-operative pain score
Post-operative Inpatient Labs: CBC w/diff if the patient remains hospitalized and is deemed clinically necessary by the surgeon
Post-operative imaging: will occur on POD7 (+/- 1 day) if the patient is still hospitalized and continues to have severe or recurrent abdominal pain, is unable to tolerate a diet, was febrile within the last 24 hours and if clinically warranted has a recent CBC with an elevated WBC.

Follow-up appointment:
Outpatient follow up Physical exam: abdominal exam
Outpatient follow up Vitals: heart rate, blood pressure, respiratory rate, pulse oximetry, temperature
Pain score

11 CRITERIA FOR EVALUATION AND ENDPOINT

11.1 Efficacy

Our study is looking to investigate the feasibility of using intra-abdominal antibiotic instillation following a successful appendectomy for acute complex appendicitis. Within this study we will investigate the incidence of deep organ space surgical site infection after a one-time dose of intra-peritoneal antibiotic instillation following a successful appendectomy for acute complex appendicitis. We will review length of stay, inpatient pain medication use, inpatient pain scores, and superficial surgical site infection of the two groups. We will also review complications and any need for further intervention. Each patient will be followed for a total of 30 days post-operatively.

12 STATISTICAL CONSIDERATIONS

A JHACH database manager will create a REDCap database for the study on the password-protected JHACH secure network. A Pediatric Surgery Research Fellow will enter data, and the Principal Investigator will check the initial data on six participants for accuracy and completeness and spot-check the data entry independently at least once a month.

All data will be checked for completeness and consistency at the end of the study. Tabular and graphical methods will be used to explore the distribution of the variables. Baseline demographic and clinical characteristics will be summarized using descriptive statistics for continuous (mean, standard deviation, median, range) and categorical variables (counts, percentages). Baseline differences between the groups will be evaluated using independent t-test or

Mann Whitney U test for continuous variables as appropriate, and Chi-squared or Fisher's exact test for categorical variables as appropriate. All statistical analyses will be performed with SAS v 9.4 or a newer version.

Analysis for Aim 1.

The primary aim of this study is to determine the feasibility and safety of the use of antibiotic solution instillation following intraoperative diagnosis of complex appendicitis. We will determine feasibility by the percentage of eligible participants who (1) agree to participate, and (2) complete all intervention sessions and measurement time points. Safety will be determined by adverse events associated with the use of intra-peritoneal antibiotic instillation for the treatment of peritonitis caused by complex appendicitis. For feasibility, we will report the proportions with corresponding 95% confidence intervals for eligibility, recruitment, enrollment, withdrawals and drop outs, and study completion. We will also collect information on barriers and issues of implementation. The study will be deemed feasible if >50% of potential participants agree to participate and at least 75% of them complete all measurement time points. These benchmarks are based on a previous similar study completed in this population. [29]. For safety we will report the incidence of adverse effect with the corresponding 95% confidence interval.

Analyses for secondary aims

We will perform an exploratory efficacy analysis to compare the antibiotic solution instillation group and the control participants on outcome measures. We will initially compare categorical outcomes using Chi-squared or Fisher's exact test as appropriate and independent t-test or Mann Whitney U test for continuous variables as appropriate. We will attempt to use logistic or linear regression as appropriate for the outcome measure to adjust for baseline characteristics that differ between the groups. The main analysis for this aim will be a modified intention-to-treat for the primary analysis. For this analysis, patients will be compared in the two arms based on how they were randomized and it will include all patients that were randomized and received surgery. We will also perform supportive per protocol and as treated analyses. Based on historical data from our institution, we anticipate that <1% of patients who are initially randomized to one arm may switch to the other arm during surgery and approximately <1% may not complete the surgery. These patients will be considered as a protocol violation and will be excluded from the per protocol analysis. The as treated analysis will group the patients according to the type of surgery they actually received and exclude those that did not complete or receive surgery. The analyses for this aim will be exploratory, as the study is not powered to detect clinically important differences between groups using these analyses. However, the findings from these analyses will be used to guide the design of a future larger study that will include appropriate sample size estimations or power analyses.

Attrition and Missing Data:

We will make every effort to reduce attrition. Missing data will be characterized and examined for non-randomness. Missing data will not be imputed.

Sample size justification:

The primary aim of this study is to assess feasibility of the proposed intervention to inform a future larger randomized controlled trial. Therefore, the sample size is not based on a power analysis. A sample size of 36 participants (18 intervention and 18 control) is appropriate to provide feasibility data that will help refine our intervention and measurements for a future larger study.[30] This sample size will allow us to estimate a conservative participation of 70% with a confidence interval of 53-87%. In a similar study conducted by the PI previously, 85% of recruited families consented to randomization and >93% of those families completed all study assessments.

Based on current estimates in our institution, we anticipate 350 appendectomies to be performed each year. Assuming the average documented 20% perforation rate, we anticipate 70 appendectomies for complicated appendicitis each year. Therefore, we will have an eligible pool of 70 patients with intra-operatively diagnosed complicated appendicitis. [29]

Study Monitoring and stopping rules:

All patients will be monitored in the post-operative period, particularly the first 48 hours following surgery. Given the study involves a single dose of intra-peritoneal antibiotic instillation any drug side effects will likely occur within the first 12 hours of treatment. At any time in the study, if a patient suffers an adverse event secondary to intra-peritoneal antibiotic instillation, all study activity will be suspended until a full investigation is completed. The study will only be reinstated after consultation with the Johns Hopkins All Children's Hospital IRB. Patients with severe allergies to cephalosporins or penicillin will be excluded from the study.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each participant that provide a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. **Data capture should be restricted to endpoints and relevant participant information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs may be monitored for completeness, accuracy, legibility and attention to detail by a member of the Regulatory Affairs / Quality Assurance department. The CRFs are completed by the Investigator or a member of the study team as listed on the Delegation of Authority log. The Investigator agrees to allow Regulatory Affairs / Quality Assurance personnel access to participants' source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Informed consent

Informed consent is obtained from all research participants and/or the legal guardian prior to performing any study procedures using the most recent IRB approved version.

14.2 Institutional Review

Research is approved by the Johns Hopkins Medicine Institutional Review Board, or other IRB of Record, as appropriate.

14.3 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period for which the IRB approval has already been given are not initiated without submission of an amendment for IRB review and approval.

These requirements for approval in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all participants included in the trial.

14.4 Protocol Deviations

A protocol deviation is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research.

The JHM IRB requires the **prompt reporting** of protocol deviations which are:

- Emergency deviations (when immediate deviations are required to protect the life or physical well-being of a participant)
- Major (representing a major change in the approved protocol), non-emergent deviation occurring without prior IRB approval

Minor or administration deviations, which do not affect the scientific soundness of the research plan or the rights, safety, or welfare of human participants, are reported to the JHM IRB at the time of continuing review.

14.5 FDA Annual Reporting

This study is being conducted under an IND submission. Therefore, annual reporting of the study's progress is required by and will be submitted to the FDA.

14.6 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the PI.

14.7 Record Keeping

As per 21 CFR 312.57, the study investigator records will be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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