PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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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VERSION 1 – REVIEW

REVIEWER	Andrew Kirby The University of Leeds England
REVIEW RETURNED	22-Feb-2017

GENERAL COMMENTS	I note this study was approved in the summer of 2016, so imagine you are underway with the trial now. So my comments, which may or may not be of interest, are probably not in time to impact on the conduct of the trial. I hope they may therefore be of general interest, and to be considered when the results of the study are written up. The protocol is well written, and clear, with the study protocol being well described. I am a microbiologist hence a number of comments have been made about the antibiotic side of the trial, and my consideration of the surgical aspects of the trial are less informed. Good luck with the trial. I will be interested to review you results in the future. Abstract • "A minority of patients eventually undergo appendectomy within a year, with 10-15% failing to respond in the initial period. " Why do you say a minority, it is somewhat subjective. I would report the figures e.g. X-Y %. I thought it was about 30% went on to appendicectomy in the next year, and I would not call this a minority number of patients. I think you agree with the 30% but you should state that number explicitly. Introduction • The comment about there being less pain and quicker return to work in the appendectomy group-is that relevant to laparoscopic surgery which is now the standard of care? Does this take account of the additional pain and time off work for the approximately 30% of patients who require late appendectomy?

	• You state that reference 12 reports a lower rate of adverse events in the antibiotic treated group, but I think this related to open surgical procedures and excluded the need for delayed surgery as a complication. From the patient perspective I would have thought they would think being re-admitted for surgery a complication. Do you think the sentence accurately reflects the trial? • You state: several did not have standardized imaging for diagnosing appendicitis leading to inclusion of patients with complicated appendicitis. It is the limited sensitivity of CT for the detection of pathological diagnosed perforations that leads to the inclusion of patients with complicated appendicitis being diagnosed as uncomplicated appendicitis, as opposed to non standard CT protocols. And does this trial have a standardised approach to imaging (CT vs MRI vs U/S). If I was in the study I would not want a unnecessary exposure to radiation (CT scan), can a patient elect not to have a CT scan? • You refer to diverticulitis as a similar condition treatable by outpatient antibiotics. It is worth noting the recently published DIABLO trial (https://www.ncbi.nlm.nih.gov/pubmed/27686365) which concluded: Observational treatment without antibiotics did not prolong recovery and can be considered appropriate in patients with uncomplicated diverticulitis. This makes me wonder if uncomplicated appendicitis is similar and also does not need antibiotics. It does question the fundamental assumption of this study that antibiotics have any efficacy in the treatment of uncomplicated appendicitis. Hypothesis • What mechanism do you think supports you hypothesis? Do you think antibiotics "cure" appendicitis i.e. that appendicitis is a bacterial infection? Or do you think antibiotics prevent progression of mild complicated appendicitis and allow time for a perforation to heal? Study population • "Included are those with imaging-confirmed acute uncomplicated appendicitis." CT scans are not able to exclude complicated appendicitis. You are including those without evidence of complicated appendicitis on imaging. "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." This seems to contradict your inclusion of only uncomplicated appendicitis (I would consider appendiceal perforation within my diagnosis of complicated appendicitis) as you include those with clinically suspected and imaging confirmed uncomplicated appendicitis. Antibiotic therapy arm • Why must patients have IV antibiotics? Some antibiotics are bioequivalent with regard their IV and PO formulations e.g. ciprofloxacin and metronidazole, clindamycin. • With regard the IDSA recommended antibiotics o Cefoxitin monotherapy may be limited by anaerobic resistance: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC127412/ o Quinolones have significant side effects and may impact on ability to drive, risks tendon damage. Will you advise patients of this when consenting? o Tigecycline has an FDA warning about an increased risk of death: https://www.fda.gov/Drugs/DrugSafety/ucm369580.htm . Will you advise patients of this when consenting?

	o Carbapenem resistance threatens to end the clinical efficacy of antibiotics; do you want to be increasing their use? Their use may theoretically put patients at increased risk of CPE (carbapenem producing Enterobacteriaceae infections .Will you advise patients of the increased risk of antibiotic resistance associated with antibiotic use when consenting? o In England we restrict the use of carbapenems to prevent the spread of CPE. o Should sites take account of local antibiotic resistance in choosing their antibiotic? o Do you want cover for only Gram negative bacteria? Not Gram positive e.g. Streptococcus milleri. o Why 10 days? We can treat other severe conditions in less e.g. meningitis in 7 days for example. o Metronidazole and clindamycin has no Gram negative cover which you previously stated was what you wanted to cover? o Oral cephalosporins are not recommended for systemic infections: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/General_documents/Oral_ceph_breakpoints_16Feb2012.pdf Event reporting: • Why is rehospitalisation for treatment of appendicitis not classified as a SAE? Other points • Is 2 year follow-up long enough to determine the impact of neoplasms not identified in the antibiotic treatment group? • I am surprised with all the patient involvement in the trial design you have not planned Discreet Choice Experiments after the trial in order to determine what intervention patients would choose based on the findings of your research. I think this would be a great opportunity to do this. Background and Rationale • "Rates of perforation were lower among those in the antibiotic treatment group. " How , if patients are randomised, can the rate of perforations be unequal between groups? https://www.ncbi.nlm.nih.gov/pubmed/25175926 • Is laparoscopic appendicectomy not now standard practice, or will it not be shortly? Is it relevant to include open procedures in the study? • Do you inform patients of the cancer risk associated with CT scans as you do for the missed neoplasia? • In the UK diagnosis is clinical, are CT/MRI/US all routine practice in the USA? • Will the non standardised approach to appendicitis diagnosis (CT vs MRI vs US) impact on thee study findings? Outcomes • The risk of antibiotic resistance is not assessed; do you think this is a relevant outcome? • Given up to 300,000 patients a year may get 10 days carbapenem therapy 3 million doses of carbapenems might be important in the spread of CPE infections in the USA. • Antibiotic consumption in the two groups is not assessed? • When you know about 15% of patients may have surgery after your 4 week primary end point assessment date this makes the end point biased to the antibiotic group whose adverse events will happen after this time point.

	The EQ-5D over at least 1 year should be the primary end point, with the EQ-5D checked when patients are re-admitted.

REVIEWER	Prof. Markus K. Diener Department of General, Visceral, and Transplanation Surgery Study Centre of the German Surgical Society (SDGC) Germany No Competing Interest
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	The Collaborative Investigators of the CODA Trial present their protocol of a rigorous comparative effectiveness trial which aims to determine, if antibiotic treatment strategy is non-inferior to appendectomy in patients with acute uncomplicated appendicitis. The study design and outcome parameters address the important questions which were already raised, but cannot be answered by the most recent systematic review and meta-analysis of Harnoss et al. (Ann Surg, 2016): Actual interest of patients, clinicians and researchers is to find an answer on patients' Quality of Life (QOL) during the two treatments and in the following course. The follow-up of two years is appropriate and will provide new information. Furthermore the investigations of "decisional regret" and analyses of subpopulations definitely help to improve patients' and physicians' decision making. Nevertheless some few aspects should be mentioned: I) Patients will all be diagnosed by CT, MRI or ultrasound and randomized also depending upon imaging findings. a. Are you investigating false-positive and false-negative diagnoses (sensitivity/ specifity of diagnostic tools)? For that it is mandatory to analyze histopathological findings. Is this routine or are you planning to do that? I believe this is absolutely mandatory. b. About 6% of patients don't have appendicitis at time of surgery (Harnoss et al., Ann Surg, 2016). Will appendectomy anyway be performed? How do you make sure that these "false-positive appendicitis" patients do not falsify/ improve the treatment effectiveness in the antibiotic treatment group? c. In case they meet the inclusion criteria, will you randomize patients who were diagnosed false-negative, but represent at the emergency department hours or days later (delayed therapy)? d. A high proportion of patients with antibiotic treatment failure develop a complicated appendicitis (progress) in the further course (Harnoss et al., Ann Surg, 2016). Are you planning to investigate the complication rate in this subgroup compared to patients immediately undergoing surgery? II) What is the time frame to perform appendectomy after randomization? Is this standardized or will you investigate that? III) You will analyze the PROMIS-Pain Intensity within the first two weeks. How do you ensure that current pain medication is not influencing your results? IV) Why do you investigate QOL first after 4 weeks of randomization? Usually patients undergoing surgery should be back to work and fully restored after 2 weeks.

	V) I believe that the antibiotic therapy options are far too broad and strong. a. If you want to investigate differences between antibiotics you will most probably not be able to answer the question which is the most effective and safe (adverse events). b. Some of the antibiotic treatment options are limited to stationary treatment. Therefore you already can't transfer your findings to the ambulatory sector (e.g. treatment by the family doctor). c. Broad-spectrum antibiotics furthermore increase the risk for resistant bacteria. Are you informing the patients about that risk at time of randomization and are you investigating that? Overall the CODA Trial is a well-planned study which will provide relevant and new information in the strategic comparison of conservative and operative treatment for acute uncomplicated appendicitis.

REVIEWER	katherine deans Nationwide Children's Hospital U.S.A
REVIEW RETURNED	19-May-2017

GENERAL COMMENTS	The CODA trial aims to identify if antibiotics alone can be used to treat appendicitis. It is a well-designed trial that is clearly articulated in this manuscript. Although the findings from this trial will be of interest broadly in the United States, my reason for rejection is that I don't think that the design of the trial is worthy of publication without results. At that time I am happy to provide a more detailed and rigorous review. In general, my bias is that there is sufficient efficacy data from around the world that antibiotics are a safe and effective treatment choice in select patients with acute uncomplicated appendicitis. I do not believe that another RCT is warranted; however, I am in the minority opinion in the U.S. Broadly, I do believe that American surgeons are interested in an American RCT to help inform their practice. This trial design has been presented at national meetings and the results are anticipated.

VERSION 1 – AUTHOR RESPONSE

Reviews and Responses:

1. “A minority of patients eventually undergo appendectomy within a year, with 10-15% failing to respond in the initial period. “ Why do you say a minority, it is somewhat subjective. I would report the figures e.g. X-Y %. I thought it was about 30% went on to appendectomy in the next year, and I would not call this a minority number of patients. I think you agree with the 30% but you should state that number explicitly.” (Page 3, line 14).

Response:
"Minority" is used for brevity in the abstract and we thank the reviewer for this perspective and have removed the word “minority” from the abstract and reported the figures as suggested.

2. “The comment about there being less pain and quicker return to work in the appendectomy group- is that relevant to laparoscopic surgery which is now the standard of care? Does this take account of the additional pain and time off work for the approximately 30% of patients who require late appendectomy?” (Page 4, line 36).

Response:
The reviewer brings up an important point. Unfortunately, prior studies nearly exclusively performed open surgery for appendicitis. The lack of standard measurement in comparing pain and disability as well as primarily open surgery are major limitations of prior studies. As described in the introduction, this trial was designed to address these limitations.

3. “You state that reference 12 reports a lower rate of adverse events in the antibiotic treated group, but I think this related to open surgical procedures and excluded the need for delayed surgery as a complication. From the patient perspective I would have thought they would think being re-admitted for surgery a complication. Do you think the sentence accurately reflects the trial?” (Page 4, line 39).

Response:
Yes, reference 12 is, "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" Page 4, line 39. We engaged patients to incorporate their perspective when designing this study and patients advised which study outcomes would best help inform treatment decisions of future patients (please see reference 23). Based on their feedback, the CODA study tracks readmission for all causes (not only for surgery) for patients in both treatment arms and, for the first time, includes longitudinal, standardized patient reported outcomes, including decisional regret (as specifically suggested by our patient partners).

4. “You state: several did not have standardized imaging for diagnosing appendicitis leading to inclusion of patients with complicated appendicitis. It is the limited sensitivity of CT for the detection of pathological diagnosed perforations that leads to the inclusion of patients with complicated appendicitis being diagnosed as uncomplicated appendicitis, as opposed to non-standard CT protocols. And does this trial have a standardised approach to imaging (CT vs MRI vs U/S). If I was in the study I would not want an unnecessary exposure to radiation (CT scan), can a patient elect not to have a CT scan?” (Page 4, line 50).

Response:
Due to the pragmatic nature of the CODA trial, there is not a standardized protocol for imaging. See manuscript: "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)".

5. “You refer to diverticulitis as a similar condition treatable by outpatient antibiotics. It is worth noting the recently published DIABLO trial (https://www.ncbi.nlm.nih.gov/pubmed/27686365) which concluded: Observational reatment without antibiotics did not prolong recovery and can be considered appropriate in patients with uncomplicated diverticulitis. This makes me wonder if uncomplicated appendicitis is similar and also does not need antibiotics. It does question the fundamental assumption of this study that antibiotics have any efficacy in the treatment of uncomplicated appendicitis.” (Page 5, line 29).

Response:
We appreciate the reviewer making this comment and highlighting this reference. We have had similar conversations with our stakeholders (clinicians and patients), and they felt strongly that there was not yet enough evidence in appendicitis to offer medical management without antibiotics for this pragmatic trial.

6. “What mechanism do you think supports you hypothesis? Do you think antibiotics “cure” appendicitis i.e. that appendicitis is a bacterial infection? Or do you think antibiotics prevent progression of mild complicated appendicitis and allow time for a perforation to heal?” (Page 6, line 37).

Response:
We thank the reviewer for this is very interesting question. As this reviewer points out, the pathophysiology of appendicitis and progression of disease is unknown. The CODA trial was not designed to address this question, so this is a topic for future studies.

7. “Included are those with imaging-confirmed acute uncomplicated appendicitis.” CT scans are not able to exclude complicated appendicitis. You are including those without evidence of complicated appendicitis on imaging.” (Page 6, line 46).

Response:
Thank you for pointing out this conflict in language and description of appendicitis. Given that there is no standard definition of "complicated" and that typically “complicated” is confirmed by surgery, we have edited the manuscript to be clear about the exclusion criteria and these are included in tracked changes.

8. “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.” This seems to contradict your inclusion of only uncomplicated appendicitis (I would consider appendiceal perforation within my diagnosis of complicated appendicitis) as you include those with clinically suspected and imaging confirmed uncomplicated appendicitis.” (Page 7, line 22).

Response:
Please see the response to comment 7.

9. “Why must patients have IV antibiotics? Some antibiotics are bioequivalent with regard their IV and PO formulations e.g. ciprofloxacin and metronidazole, clindamycin.” (Page 9, line 7).

Response:
We choose initial IV antibiotics because our clinical stakeholders were concerned about poor tolerance and adherence of PO medications alone given the large proportion of patients with appendicitis that have significant nausea on presentation to the emergency department. In our experience and in Dr. Talan's appendicitis pilot we demonstrated good subsequent antibiotic adherence and outcomes with this approach (please see reference 22). Therefore, after initiation of IV therapy, switching to PO for those who can tolerate it is encouraged in the CODA trial.

10. "With regard the IDSA recommended antibiotics:
a. Cefoxitin monotherapy may be limited by anaerobic resistance:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC127412/
b. Quinolones have significant side effects and may impact on ability to drive, risks tendon damage. Will you advise patients of this when consenting?
c. Tigecycline has an FDA warning about an increased risk of death:
https://www.fda.gov/Drugs/DrugSafety/ucm369580.htm. Will you advise patients of this when consenting?
d. Carbapenem resistance threatens to end the clinical efficacy of antibiotics; do you want to be increasing their use? Their use may theoretically put patients at increased risk of CPE (carbapenem producing Enterobacteriaceae infections .Will you advise patients of the increased risk of antibiotic resistance associated with antibiotic use when consenting?
e. In England we restrict the use of carbapenems to prevent the spread of CPE.
f. Should sites take account of local antibiotic resistance in choosing their antibiotic?
g. Do you want cover for only Gram negative bacteria? Not Gram positive e.g. Streptococcus milleri.
h. Why 10 days? We can treat other severe conditions in less e.g. meningitis in 7 days for example.
i. Metronidazole and clindamycin has no Gram negative cover which you previously stated was what you wanted to cover?
j. Oral cephalosporins are not recommended for systemic infections:
http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/General_documents/Oral_ceph_breakpoints_16Feb2012.pdf" (Page 9, line 10).

Response:
We choose antibiotic regimens that were recommended by US professional organization guidelines (IDSA and SIS) for treatment of intra-abdominal infections, which are consistent with the World Society of Emergency Surgery (WSES) guidelines. We appreciate the thoughtful consideration of each antibiotic listed. Given the pragmatic nature of the trial, we determined that offering any of the recommended regimens was appropriate and all site PIs reference their local antibiotograms to determine if additional consideration should be given in their population (e.g., E. coli resistance). We anticipate analysis of treatment effect in different antibiotic classes following the final study results. We also anticipate subpopulation analysis to examine the length of time of therapy (compliance) and different antibiotic regimens used. Risks of both arms of the study is included in the consent, video, and discussed per routine care with the emergency medicine and surgical providers.

11. "Why is rehospitalisation for treatment of appendicitis not classified as a SAE?" (Page 10, line 56.)

Response:
We recognize that events resulting in inpatient hospitalization or prolongation of hospitalization are typically classified as SAEs. We expect, based upon previous studies, that up to 30% of patients treated with antibiotics could be rehospitalized for treatment of appendicitis. We had numerous discussions with our clinician and patient advisors when designing this study and determined that the intent of the SAE reporting for CODA is to capture life-threatening events (toxic megacolon, ICU admission for bleeding, etc.) in both study arms.

We do not anticipate that rehospitalization for appendicitis will be life-threatening. We are capturing and will report rehospitalization for all causes (including recurrent appendicitis) as this is also a critical event to report. We also have an independent Data Safety Monitoring Board that will monitor the rates of rehospitalization for all causes (including recurrent appendicitis) to ensure patient safety.

12. “Rates of perforation were lower among those in the antibiotic treatment group.“ How, if patients are randomised, can the rate of perforations be unequal between groups? https://www.ncbi.nlm.nih.gov/pubmed/25175926”

Response:
This quoted sentence cannot be found in our original text and it is unclear to us what the reviewer is referring to in the CODA protocol paper. We would also expect that the rates of initially perforated appendicitis cases be equal in a previous randomized trial.

13. “Is laparoscopic appendicectomy not now standard practice, or will it not be shortly? Is it relevant to include open procedures in the study?”

Response:
Given the pragmatic nature of the study we felt it was important to include all forms of appendectomy in the US, accepting that laparoscopic is by far the most common.

14. “Do you inform patients of the cancer risk associated with CT scans as you do for the missed neoplasia? In the UK diagnosis is clinical, are CT/MRI/US all routine practice in the USA?” (Page 26, line 20).

Response:
Preoperative imaging is the standard in the US. The CODA study does not require CT imaging and US is acceptable. Physicians provide their usual informed consent for care including advising on CT risk which is completed prior to CODA recruitment.

15. Will the non standardised approach to appendicitis diagnosis (CT vs MRI vs US) impact on these study findings? a.
a. Are you investigating false-positive and false-negative diagnoses (sensitivity/ specificity of diagnostic tools)? For that it is mandatory to analyze histopathological findings. Is this routine or are you planning to do that? I believe this is absolutely mandatory.
b. About 6% of patients don’t have appendicitis at time of surgery (Harnoss et al., Ann Surg, 2016). Will appendectomy anyway be performed? How do you make sure that these “false-positive appendicitis” patients do not falsify/ improve the treatment effectiveness in the antibiotic treatment group?
c. In case they meet the inclusion criteria, will you randomize patients who were diagnosed false-negative, but represent at the emergency department hours or days later (delayed therapy)?
d. A high proportion of patients with antibiotic treatment failure develop a complicated appendicitis (progress) in the further course (Harnoss et al., Ann Surg, 2016). Are you planning to investigate the complication rate in this subgroup compared to patients immediately undergoing surgery?” (Page 26, line 39).

Response:
A) Yes, imaging correlation with intraoperative findings and pathology will be examined.
B) It is standard surgical practice in the US that patients have an appendectomy even if the appendix appears "normal" intraoperatively. Given the nature of the RCT, we anticipate an equal number of patients with falsely positive diagnosed appendicitis in both treatment arms of the randomized cohort.

C) We randomize all patients meeting entry criteria when they present to the ED and only exclude them if antibiotic therapy was started more than 7 hours prior to ED presentation. We are tracking the time from initial symptom presentation.
D) Yes.

16. “When you know about 15% of patients may have surgery after your 4 week primary end point assessment date this makes the end point biased to the antibiotic group whose adverse events will happen after this time point. The EQ-5D over at least 1 year should be the primary end point, with the EQ-5D checked when patients are re-admitted.” (Page 41, line 11).

Response:
We anticipate that complications from both arms are likely to occur within 30 days and therefore, this was an ideal time point for comparing EQ-5D. However, we agree that there are critical secondary endpoints including recurrent disease and complications from surgery that will take place in the following years from initiation of treatment and they will be reported as well.

17. “The risk of antibiotic resistance is not assessed; do you think this is a relevant outcome?; Antibiotic consumption in the two groups is not assessed?; Given up to 300,000 patients a year may get 10 days carbapenem therapy 3 million doses of carbapenems might be important in the spread of CPE infections in the USA.” (Page 41, line 41).

Response:

We agree this is an important aspect of changing the treatment paradigm for patients. The treatment of patients with an imaging-supported diagnosis of appendicitis is targeted antibiotic treatment for a limited amount of time involving generally heathy community-dwelling adults. Therefore, the impact of increased antibiotic use on individuals or communities is expected to be small relative to indiscriminant antibiotic use for UTIs and through human exposure to antibiotics in food animals. We will follow participants for antibiotic-related AEs and subsequent infections but will not be able to measure the impact on community resistance patterns in this trial.

18. “Is 2 year follow-up long enough to determine the impact of neoplasms not identified in the antibiotic treatment group?” (General comment).

Response:
The CODA study will stop at the completion of the PCORI contract and we hope that future funding will allow us to continue to monitor longer term outcomes of the CODA patients (e.g. development of neoplasia, small bowel obstruction, hernia formation, chronic abdominal pain).

19. “I am surprised with all the patient involvement in the trial design you have not planned Discreet Choice Experiments after the trial in order to determine what intervention patients would choose based on the findings of your research. I think this would be a great opportunity to do this.” (General comment).

Response:
Thank you, this is an excellent suggestion and will certainly be the subject of future studies.

20. “What is the time frame to perform appendectomy after randomization? Is this standardized or will you investigate that?” (General comment).

Response:
Due to the pragmatic nature of the CODA trial we defer to usual surgical practice (during the index admission) for timing of the operation for those in the surgical cohort. The time from initial presentation and treatment is monitored.

21. “You will analyze the PROMIS-Pain Intensity within the first two weeks. How do you ensure that current pain medication is not influencing your results?” (General comment).

Response:
We anticipate a wide range of pain score and medication requirements for pain control. We are using the PROMIS-pain intensity scale and questions on medication requirements (e.g. narcotic requirements) to help describe that variation.

22. “Why do you investigate QOL first after 4 weeks of randomization? Usually patients undergoing surgery should be back to work and fully restored after 2 weeks.” (General comment).

Response:
Additional information on pain, work productivity, medication use are measured weekly in addition to the EQ5D at 4 weeks.

23. “I believe that the antibiotic therapy options are far too broad and strong.” (General comment).

Response:
The protocol-recommended antibiotics are based on the most recent Infectious Diseases Society of America and Surgical Infectious Society management guidelines and reflect standard accepted practice in the U.S. While there is evidence supporting short-course antibiotic treatment of patients with complicated intra-abdominal infections who have received source control, there are insufficient data to fully inform the duration of antibiotic treatment for medical management acute uncomplicated appendicitis and, therefore, we chose a 10-day duration based on regimens used in previously published studies.

24. “If you want to investigate differences between antibiotics you will most probably not be able to answer the question which is the most effective and safe (adverse events).” (General comment).

Response:
We agree. This is not a trial in which patients randomized to medical treatment are further randomized to various antibiotic regimens. This aspect of the trial is pragmatic, however, we plan to do exploratory analysis of outcomes and adverse events related to various regimens.

25. “Some of the antibiotic treatment options are limited to stationary treatment. Therefore you already can’t transfer your findings to the ambulatory sector (e.g. treatment by the family doctor).” (General comment).

Response:
We are not familiar with the term, "stationary treatment." However, we agree that our study would not model the practice of a presumptive clinical diagnosis of acute uncomplicated appendicitis and office-based, presumably, medical treatment (although maybe this would be a future option). At the present time, standard US practice is referral of all patients with suspected appendicitis to an emergency department and then the diagnosis is typically confirmed with some type of imaging, mostly CT, but more frequently ultrasound especially in younger, low body weight patients.

In emergency departments, parenteral antibiotics can be administered, and our protocol requires 24-hours of IV antibiotics based on the rationale that patient oral antibiotic adherence might be initially compromised early in the course of their intra-abdominal infection. Use of long-acting regimens also facilitates outpatient arrangement, which has recently been demonstrated to be safe in selected patients (please see reference 22).

26. “Broad-spectrum antibiotics furthermore increase the risk for resistant bacteria. Are you informing the patients about that risk at time of randomization and are you investigating that?” (General comment).

Response:
The comment suggests that the patient would be at increased risk of antibiotic resistant bacteria from a 10-day vs. peri-operative duration of antibiotic treatment (the spectrum of these regimens is similar). While greater exposure to antibiotics has been shown to result in selection of more antibiotic resistance flora, the risk of an antibiotic-resistant infection is a product affected by the risk of developing a subsequent infection. First, previous studies have consistently demonstrated that medical treatment results in fewer complications, specifically wound infections (since there were fewer wounds in the non-surgically treated patients). Second, the epidemiology of appendicitis reflects disease predominately in healthy young persons, who are typically less prone to infection. Third, there is no evidence from previous trials that antibiotic-treated patients who either have initial antibiotic failure or subsequent recurrence of appendicitis suffer complications related to inability to treat an antibiotic resistant infection. Fourth, as per our protocol, as opposed to routine hospitalization of surgery-randomized patients, many stable antibiotic-randomized patients will be discharged home from the emergency department and not hospitalized and exposed to antibiotic resistant hospital flora and other hospital-associated microbial threats like C. difficile. Given this, we are not informing patients of a potential risk for resistance with randomization to either arm.

We appreciate the comments from the reviewers and the opportunity to revise this manuscript. Thank you for taking the time to review our manuscript.

VERSION 2 – REVIEW

REVIEWER	Andrew Kirby Associate Clinical Professor in Microbiology The University of Leeds England
REVIEW RETURNED	19-Jul-2017

GENERAL COMMENTS	In the review checklist I have answered the study design is appropriate. But I do have concerns over the choice of primary outcome measure which I don't think will capture events after the 1 month period which are known to be significant, and will not capture poor quality of life prior to the 1 month date. “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.” I still disagree with this sentence-it depends on how you define complications. If you want to add this sentence I would suggest you qualify what is/is not included in the definition of complications.

	"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." I am unsure why you highlight this as a limitation of previous trials when you are not planning standardised imaging in the CODA trial. Exclusion criteria: Do you have a definition of septic shock? Including patients in such a trial who have appendiceal perforation has not been done before and would not be an approach I would favour. When there is a 15% failure rate in 1 month in patients who are not believed to have perforations there is potential for there to be a high failure rate in this group. I think it will be important that the data management committee is able to analyse outcomes in this patient group to limit potential harm. Participant Assessment Schedule. The follow up here is bias to antibiotic treatment as work productivity will not capture the 15% (approx.) of patients who would be expected to have an appendicectomy after 3 months Primary outcome "The primary outcome for the CODA trial is the EQ-5D index reported four weeks" When I have discussed the use of the EQ-5D with health economists they have explained that the quality of life across a time period is important i.e. a single time point may be meaningless to describe care over a time period. I would suggest discussion with your health economist to ensure your primary outcome measure is not rejected by those reading your trial results. I personally would not accept non-inferiority of a single time point EQ-5D (1 month) as a reason to change practice. I would be looking at 1/2 year outcomes as lots of surgery happens after 1 month as well. Agreeing primary outcome measures is difficult, but I am not sure you are there yet. How are you ensuring a IDSA/SIS recommended regimen is going to be prescribed and that a regimen specifically not recommended e.g. Cephalosporin-based regimens and cephalosporin–β-lactamase inhibitor combinations • Do not use cefoxitin and cefotetan routinely for empiric therapy (Grade 2-B). • Do not use cefazolin plus metronidazole routinely for empiric therapy (Grade 2-C). Prescribing antibiotic regimens for intra-abdominal infection which have no Gram negative or Gram positive cover would be something I would not be normally do, but I appreciate you are somewhat limited by the limitations of your national guidelines.

REVIEWER	Markus Diener University Hospital Heidelberg, Department of Surgery, Heidelberg, Germany
REVIEW RETURNED	02-Aug-2017

GENERAL COMMENTS	The authors present the protocol of a well planned and described trial. There is no need of further corrections.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Andrew Kirby
Institution and Country: Associate Clinical Professor in Microbiology, The University of Leeds, England

Comment: In the review checklist I have answered the study design is appropriate. But I do have concerns over the choice of primary outcome measure which I don't think will capture events after the 1 month period which are known to be significant, and will not capture poor quality of life prior to the 1 month date.

Response
The CODA study will capture events for both quality of life as well as clinical events for up to two years. See section “Outcomes and Measures”. Sentence structure is changed to ensure this is clear.

Comment: “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” I still disagree with this sentence-it depends on how you define complications. If you want to add this sentence I would suggest you qualify what is/is not included in the definition of complications. (Page 3, line 39).

Response:
Thank you- the manuscript is updated to more specifically reflect the post-intervention complication specifically described in Dr. Salminen’s paper and summarized in APPAC trial table 3 and is the data referred to and cited in this sentence.

Comment: “…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.” I am unsure why you highlight this as a limitation of previous trials when you are not planning standardized imaging in the CODA trial. (Page 4, line 24).

Response:
Nearly all patients with suspected appendicitis in the United States are imaged, but it is variable if ultrasound or CT are completed based on individual hospital resources and patient factors (such as BMI). The design of the CODA trial is pragmatic to include the variability in ways that patients are diagnosed in the US. The diagnostic work up in prior trials are mentioned in this paper to describe to the reader the reasons that the CODA protocol was developed to include patients with appendicolith.

Comment: Exclusion criteria: Do you have a definition of septic shock?

Response:
The definition used for the exclusion criteria is: new presumed sepsis-related organ dysfunction, elevated lactate, and/or fluid unresponsive hypotension and this was added to the protocol paper.

Comment: Including patients in such a trial who have appendiceal perforation has not been done before and would not be an approach I would favour. When there is a 15% failure rate in 1 month in patients who are not believed to have perforations there is potential for there to be a high failure rate in this group. I think it will be important that the data management committee is able to analyze outcomes in this patient group to limit potential harm. (Page 5, line 56).

Response:
We are including patients with appendiceal perforation given that data for imaging is inaccurate and CTs that are read as uncomplicated appendicitis actually miss up to 25% of perforations found at operation. Undoubtedly, many such patients were actually included in past trials (where there was no imaging used). We anticipate looking at clinical (including radiographic) features that are associated with antibiotic failure and previously described outcomes. The Data Safety Monitoring Board (independent of the clinical team) reviewed and approved the protocol including inclusion criteria, safety monitoring plans, and meets quarterly to assess the safety of the study.
Participant Assessment Schedule. The follow up here is bias to antibiotic treatment as work productivity will not capture the 15% (approx.) of patients who would be expected to have an appendicectomy after 3 months. (Page 8, line 44).

Response:
We appreciate this assessment and agree that those that have recurrent disease may have additional time away from work/school and decreased productivity following the 3 months period. The inclusion of EQ-5D at later time points as a part of the primary outcome would have the tendency of biasing towards non inferiority of antibiotics treatment since we expect the two treatment groups to have similar quality of life 1 and 2 years later, when the majority of participants will not have had appendicitis within the last 3 months. Moreover, we limited the repetition of surveys in concern for participant survey burden and had additional concern that measurement of EQ-5D too far in the future may be impacted by other, external factors (such as new illness or job loss). EQ-5D and the secondary QOL outcomes will be analyzed and compared across groups for the initial 3 months , as well as the later follow-up time points of 1 and 2 year. Any recommendation provided by the study team would be based on data from multiple QOL of measures collected at several time points.

Comment: “The primary outcome for the CODA trial is the EQ-5D index reported four weeks” When I have discussed the use of the EQ-5D with health economists they have explained that the quality of life across a time period is important i.e. a single time point may be meaningless to describe care over a time period. I would suggest discussion with your health economist to ensure your primary outcome measure is not rejected by those reading your trial results. I personally would not accept non-inferiority of a single time point EQ-5D (1 month) as a reason to change practice. I would be looking at 1/2 year outcomes as lots of surgery happens after 1 month as well. Agreeing primary outcome measures is difficult, but I am not sure you are there yet. (Page 10, line 55).

Response
The primary outcome (EQ-5D at 90 days following treatment) was selected because it has been used as a summary measure of disease and treatment effect in prior studies of appendicitis (see reference 31 of the manuscript), it has been widely used in other medical condition and it is responsive to surgical treatment. After prior RCTs, Patient and Clinician Advisors felt that the EQ-5D incorporate the domains likely to be impacted by surgery or a non-surgical intervention of similar effectiveness and did not feel that the clinical efficacy of antibiotics was the only relevant outcome. We will be reporting on other important secondary outcomes earlier and through the second year. We appreciate this concern and agree that there are advantages and disadvantages to picking timepoints both earlier and later than that which we chose for our primary outcome.

Comment: How are you ensuring a IDSA/SIS recommended regimen is going to be prescribed and that a regimen specifically not recommended e.g. Cephalosporin-based regimens and cephalosporin–β-lactamase inhibitor combinations do not use cefoxitin and cefotetan routinely for empiric therapy (Grade 2-B). Do not use cefazolin plus metronidazole routinely for empiric therapy (Grade 2-C). (Page 9, line 12).

Response:
The 2010 IDSA/SIS guidelines, which were available when the protocol was written grade cefoxitin or cefazolin plus metronidazole as A-1 for "mild-to-moderate community-acquired IAA," so we allow these regimens. See:

"…For adult patients with mild-to-moderate community-acquired infection, the use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as a single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-Pseudomonal activity (Table 2) (A-I)." (Clin Infect Dis. 2010;50:133-164).

The 2017 SIS guidelines (which were not released while the protocol was started) acknowledge a high rate of E. coli susceptibility to both cefoxitin and cefazolin in North America, which is where the CODA trial is conducted (Surg Infect. 2017;18. DOI:10.1089/sur.2016.261).
Each hospital site is educated on the recommended antibiotics and course, antibiotic prescriptions are auditing and reported when deviating from protocol, and compliance with taking medication as prescribed is asked in survey of participants.

Comment: Prescribing antibiotic regimens for intra-abdominal infection which have no Gram negative or Gram positive cover would be something I would not be normally do, but I appreciate you are somewhat limited by the limitations of your national guidelines. (General).

Response:
The antibiotic regimens recommended do have appropriate Gram negative and some Gram positive activity that covers the most common appendicitis organisms.

Reviewer: 2
Reviewer Name: Markus Diener
Institution and Country: University Hospital Heidelberg, Department of Surgery, Heidelberg, Germany
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comment: The authors present the protocol of a well planned and described trial. There is no need of further corrections.

Response: Thank you

VERSION 3 – REVIEW

REVIEWER	Andrew Kirby The University of Leeds, England.
REVIEW RETURNED	07-Sep-2017

GENERAL COMMENTS	Thank you for considering my previous comments in your review. I have additional comments, below, which are essentially on the same subjects as before i.e. I have no new comments. Therefore after this review I do not have any additional comments and wish the authors success in their clinical trial. I think we still disagree about the APAAC trial. I consider this trial does not support the routine use of antibiotics for appendicectomy, the authors themselves state."Because we established a 24% minimal clinically important difference, we did not demonstrate noninferiority of antibiotic treatment for appendicitis relative to surgical treatment. I think you have looked at the secondary complications and considered these numbers as the post-intervention complications. The secondary complications in this study exclude the primary outcome measure. I would suggest adding all complications (primary and secondary outcomes) before concluding there was a lower rate of post intervention complications. The justification for including patients with CT confirmed perforation seems to be that this happened in previous trials. The important point though is that in previous trials efforts were made to exclude patients with perforations , but there were false negative imaging reports i.e. patients with perforations were unintentionally included. Radiologically detected perforations are likely to be significantly more advanced than those detected histologically, I would guess. I am pleased you have mitigated these risks with safety monitoring plans. EQ-5D. Sorry, I don't think I explained my thoughts well on the last review. I was thinking you would have the EQ-5D as your primary outcome measure. But that you would take measurements through the year as planned, and then take the area under the curve of the quality of life scores across the year (assuming it is the VAS component of the EQ5D score you are using). Which part of the EQ-5D is the primary measure? Re: Antibiotic choices. I would have thought it appropriate to update these as guidelines are updated through protocol amendments. And clindamycin and metronidazole as an oral regimen is not a regimen that has Gram negative cover.

VERSION 3 – AUTHOR RESPONSE

Comment: Thank you for considering my previous comments in your review. I have additional comments, below, which are essentially on the same subjects as before i.e. I have no new comments. Therefore after this review I do not have any additional comments and wish the authors success in their clinical trial.

Response: Thanks you for the review of our protocol and comments.

Comment: I think we still disagree about the APAAC trial. I consider this trial does not support the routine use of antibiotics for appendicectomy, the authors themselves state. "Because we established a 24% minimal clinically important difference, we did not demonstrate noninferiority of antibiotic treatment for appendicitis relative to surgical treatment.

Response: The manuscript reflects the post-intervention complication of the APAAC trial.

Comment: I think you have looked at the secondary complications and considered these numbers as the post-intervention complications. The secondary complications in this study exclude the primary outcome measure. I would suggest adding all complications (primary and secondary outcomes) before concluding there was a lower rate of post intervention complications.

Response: We appreciate this assessment, and have no changes or revisions to the protocol.

Comment: The justification for including patients with CT confirmed perforation seems to be that this happened in previous trials. The important point though is that in previous trials efforts were made to exclude patients with perforations, but there were false negative imaging reports i.e. patients with perforations were unintentionally included. Radiologically detected perforations are likely to be significantly more advanced than those detected histologically, I would guess. I am pleased you have mitigated these risks with safety monitoring plans.

Response: Thank you for your comment, we have no changes or revisions to the protocol.

Comment: EQ-5D. Sorry, I don't think I explained my thoughts well on the last review. I was thinking you would have the EQ-5D as your primary outcome measure. But that you would take measurements through the year as planned, and then take the area under the curve of the quality of life scores across the year (assuming it is the VAS component of the EQ5D score you are using). Which part of the EQ-5D is the primary measure?

Response: The EQ-5D index is the primary outcome measure and not the VAS. The EQ-5D index maps the response to each of 5 questions (dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression) into one of 243 health states. The score ranges from -0.11 to 1.0, with qualitative anchors at 0 (= death) and 1 (= perfect health).
The reason we do not plan to consider the area under the curve over the follow-up period as a primary analysis is that we anticipate the average EQ-5D index scores between the two randomized groups will converge over time. In a non-inferiority testing framework, this will have the tendency towards declaring non-inferiority (our alternative hypothesis) if one averages long-term quality of life with the short-term quality of life. Instead, we designed the study around evaluating quality of life at the earliest time when symptom resolution of the initial event should have occurred. We will, of course, measure and describe the EQ-5D index scores between groups in our primary outcomes. Thank you for allowing us to clarify this important point.

Comment: Re: Antibiotic choices. I would have thought it appropriate to update these as guidelines are updated through protocol amendments. And clindamycin and metronidazole as an oral regimen is not a regimen that has Gram negative cover.

Response: We do not have a protocol recommended antibiotic regimen consisting of clindamycin or metronidazole alone or together.