PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Initial non-operative management of uncomplicated appendicitis in children: A protocol for a multicenter randomized controlled trial (APAC trial)
AUTHORS	Knaapen, Max; van der Lee, Johanna H.; Bakx, Roel; The, Sarah-May; Van Heurn, Ernst; Heij, Hugo; Gorter, Ramon; ., APAC collaborative study group

VERSION 1 – REVIEW

REVIEWER	Simon Eaton UCL Great Ormond Street Institute of Child Health SE is an investigator on the APPY trial and the CONTRACT Trial, both of which have similarities to this study design.
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	This is a protocol for an RCT of conservative treatment of acute uncomplicated appendicitis in children. The RCT is timely and well-designed, following on from a previous pilot by the same group, and the protocol in general is clear and well-written. The trial has already commenced so major amendments are not feasible; however I have the following specific comments: The authors quote a rate of 68-90% of uncomplicated appendicitis in children and state that this is higher than adults but do not provide a figure for adults. A figure and reference for adults would be useful. The authors cite 4 ongoing RCTs in children. However, one of these (that of Minnecci et al. NCT02271932) is not an RCT but a preference study in which parents and children choose whether to have an operation or not. Please correct. The power calculation is based on a non-inferiority study design assuming a 10% rate of complications in the operative group, and a 5% non-inferiority margin, so that the complication rate in non-operative treatment should lie between 5 and 15% - although the power calculation is one-sided so that I presume that NOT is assumed to have a higher rate of complications?. The authors do not provide any justification for these numbers in either group. (e.g. baseline data from their own centres, or published data). In addition the paragraph describing the power calc/non-inferiority margin is written confusingly. This paragraph is the central paragraph of the trial design so it is crucial that it is absolutely clear. The non-inferiority margin should also be mentioned in the abstract. The authors state that 'Delayed appendectomy is not considered a complication, as we consider appendectomy necessary in patients who do not respond to initial non-operative management.'

	However, there is no mention here of patients who have recurrent appendicitis following initial resolution and discharge. Again, the definitions of what is, and what is not to be regarded as a complication, is absolutely key to this trial. I assume from the lists of included complications that follow, that recurrent appendicitis is not a complication. However, it would be good to be absolutely explicit about this. Hernia cicatrialis is not a commonly used term in Medical English (or at least not one that I'm familiar with)– I assume this is an incisional hernia? Although 'Total length of hospital stay during the follow-up period for complications related to the allocated treatment' is listed as a secondary outcome, length of the initial hospital stay is not included, although this is an important outcome in its own right, as well as a contributor to the cost analyses. The discussion does not include a section about faecoliths, although this is an exclusion condition worthy of further explanation. In addition, the discussion seems to stop rather abruptly without a summing-up sentence or paragraph. In conclusion, this is a worthwhile trial of an important issue, but there are areas of importance that need further clarity.

REVIEWER	Paulina Salminen Turku University Hospital and Turku University, Turku, Finland
REVIEW RETURNED	01-Jul-2017

GENERAL COMMENTS	The authors present a study protocol aiming to evaluate the effectiveness of the initial non-operative treatment strategy compared to immediate appendectomy in children in terms of complications (primary endpoint), health-related QOL and costs. There is a clear need for RCTs in the treatment of uncomplicated acute appendicitis in the pediatric population comparing non-operative antibiotic treatment with appendectomy. The APAC trial tries to add information on this important topic. Major concerns: 1. The authors have based the trial on the argument that both treatment strategies are 100% effective in treating appendicitis as non-operative therapy is converted into appendectomy in cases of unsuccessful treatment or recurrence. a. This is a very practical and clinical approach as in real life this is what happens. However, I am not sure, whether this is either statistically or form a clinical perspective the optimal setting especially with the primary endpoint being complication rate. b. The authors have stated to perform both ITT and PP analysis, but with a primary endpoint of complication rate, with this trial setting I am concerned for bias in the NOT group 2. Definitions of the primary outcome in both study groups need to be much more precise in order to enable reliable comparison a. It is good that delayed appendectomy is not considered a complication (please see 1.) as it is not in this respect evaluating the possibility of treating most of the patients with uncomplicated acute appendicitis with antibiotics instead of surgery.

	b. Define allergic reaction; rash? c. SSI definitions need to be precise and validated d. Bowel obstruction, imaging or clinical diagnosis or both? e. Other antibiotic related problems? Diarrhoea? Other abdominal symptoms related to antibiotic use? Nausea? etc. f. Appendectomy complications: Clavien-Dindo score? Minor concerns: 1. NOT is not a good abbreviation for non-operative treatment and the abbreviation should be discarded and write out the term 2. In the methods section in addition to multiple meta-analysis and the Frech trial, the authors should discuss all of the excisting RCTs on the topic in the adult population including the Swedish studies by Styrud and Hansson and our Finnish APPAC trial. The evaluation of the primary endpoint and the definitions is good to do based on the excisiting literature. 3. APAC trial acronym is very close to our APPAC trial acronym and maybe it would be beneficiary to APAC-study to somehow revise their acronym to better state the pediatric patient population in the trial name to be more informative and avoid unnecessary mix-ups. 4. Appendicolith definition in the ultrasound imaging, us criteria for appendicolith? 5. More information on the parallel implementation study needs to be stated in the study protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1: “The authors quote a rate of 68-90% of uncomplicated appendicitis in children and state that this is higher than adults but do not provide a figure for adults. A figure and reference for adults would be useful.”

Response 1: Exact data on the rate of uncomplicated appendicitis across ages is scarce. Unpublished data from the Netherlands, revealed that the incidence of uncomplicated appendicitis was 70% in 523 children. (Bolmers et al. in the thesis by van Rossem available at https://pure.uva.nl/ws/files/2725188/173229_03.pdf). However in this study the incidence of uncomplicated appendicitis was significantly lower (30%) in children below the age of 6 years. Recently, similar numbers in the adult population have been reported from the snapshot study performed in the Netherlands (van Rossem et al. 2016 BJS). The exact number of uncomplicated and complicated appendicitis according to different age groups is not provided in this study. It was however already noted in 2003, that in the adult population, the rate of uncomplicated appendicitis declines with increasing age. We added the reference and adjusted the phrasing:

Page 3 Line 39: “Approximately one third of all cases of appendicitis occur under the age of 20 years. Regarding the distribution of uncomplicated and complicated appendicitis in the pediatric population, the percentage of uncomplicated appendicitis is reported to range between 68-90% in children aged 5 to 18 years (2,11). The percentage of complicated appendicitis increases with age (12), therefore reducing the amount of patients suitable for initial non-operative treatment strategy. Potential benefits of initial non-operative treatment strategy might be therefore higher for the pediatric population than for the adult population.“

12. Al-Omran M, Mamdani M, McLeod RS. Epidemiologic features of acute appendicitis in Ontario, Canada. Can J Surg. Canadian Medical Association; 2003 Aug;46(4):263–8.

Comment 2: “The authors cite 4 ongoing RCTs in children. However, one of these (that of Minnecci et al. NCT02271932) is not an RCT but a preference study in which parents and children choose whether to have an operation or not. Please correct.”

Response 2:. We corrected it accordingly.

Page 4 Line 12: “As of today, apart from the trial described in this article, four large clinical studies are recruiting children for a comparison of primary appendectomy with NOT. Three RCTs(12–14) and one patient preference prospective case control study(15).”

Comment 3: “- although the power calculation is one-sided so that I presume that NOT is assumed to have a higher rate of complications? “

Response 3: This study is designed as a non-inferiority study. Appropriate in these types of studies is a one-sided test. We want to study if the null hypothesis that NOT is inferior to appendectomy defined as a complication rate of more than 5% worse than appendectomy can be rejected. There is no need to test whether the complication is more than 5% better than appendectomy, which would indicate superiority. So a 2-sided test is not necessary.

Comment 4: “The authors do not provide any justification for these numbers in either group. (e.g. baseline data from their own centers, or published data). In addition the paragraph describing the power calculation/non-inferiority margin is written confusingly. This paragraph is the central paragraph of the trial design so it is crucial that it is absolutely clear. The non-inferiority margin should also be mentioned in the abstract.”

Response 4: The paragraph is re-written according to your comments made and hopefully is more understandable. We added the basis for the complication rate assumed in the power calculation. This is unpublished data from a parallel cohort of patients who refused to participate and declined antibiotic treatment and underwent appendectomy in our pilot study. The non-inferiority margin was added to the abstract.

Page 5 Line 39: “A non-inferiority design is used based upon the notion that NOT potentially has secondary advantages, for instance cost reduction and less pain(26). We hypothesize that this might also be the case for QoL. It would thus be sufficient to demonstrate that the outcome in terms of complications is not worse in the NOT group compared to the immediate appendectomy group.
In our pilot study(27) we followed the children eligible for non-operative treatment who refused participation in that study and received immediate appendectomy instead of antibiotic treatment. The frequency of post-operative complications in this group at 1-year follow-up was approximately 10% (unpublished data), meaning that 90% was successfully treated without complications in the operative group. If the difference in complication rate between NOT and operative treatment is less than 5% in favour of appendectomy, non-inferiority is assumed. We will not be testing for the superiority of NOT. Using a 1-sided alpha of 2.5% in accordance with the non-inferiority design, 150 patients per group are needed to achieve 90% power for the exclusion of a difference in favour of the usual care group of more than 5%. Although in our pilot study (27) the drop-out rate after one year was only 2%, we take into account a drop-out rate of 10%. Therefore, the number of patients to be included is 334.”

Comment 5: “there is no mention here of patients who have recurrent appendicitis following initial resolution and discharge. --- However, it would be good to be absolutely explicit about this”

Response 5: We have now explicitly reported why we do not consider a delayed appendectomy as a complication. We also added a part in our discussion section to further explain our choice primary outcome.

Method section:
Page 8 Line 7: “Any form of delayed appendectomy is not considered a complication, as we consider appendectomy necessary in patients who do not respond to initial non-operative management. This includes early failure during initial admission but also recurrent appendicitis after initial discharge. Complications as a result of a delayed appendectomy are included in the primary outcome.”

Discussion section
Page 11 Line 38: “Determining the appropriate primary outcome measure in studies comparing non-operative treatment versus operative treatment remains challenging. In our opinion, both strategies will be effective in treating patients with appendicitis, and therefore effectiveness or failure is not an appropriate outcome measure. Therefore we decided to use a composite outcome measure i.e. complications. Such outcome measures (morbidity and mortality) are necessary in order to start the debate whether or not non-operative treatment strategy can be integrated in clinical practice. Furthermore our goal is to compare the initial non-operative treatment strategy (reserving an appendectomy for those not responding or with recurrent appendicitis) to direct operative treatment strategy. In this view, stating that a delayed appendectomy for the indication of failed antibiotic treatment or recurrent appendicitis is a complication would not be appropriate as it is integrated in the treatment strategy. Post-operative complications after a delayed appendectomy are however considered as complications of the initial non-operative treatment strategy. The amount of delayed appendectomies (for both non-responders and recurrent appendicitis) needs to be included in the debate whether or not initial non-operative treatment strategy is feasible. It is therefore reported as a secondary outcome.”

Comment 6: “Hernia cicatrialis is not a commonly used term in Medical English (or at least not one that I’m familiar with)– I assume this is an incisional hernia?”

Response 6: The term has been altered to incisional hernia throughout the manuscript.

Comment 7: “Although ‘Total length of hospital stay during the follow-up period for complications related to the allocated treatment’ is listed as a secondary outcome, length of the initial hospital stay is not included, although this is an important outcome in its own right, as well as a contributor to the cost analyses.”

Response 7: This outcome was indeed not properly formulated. The text was revised.

Page 9 Line 20: “Total length of hospital stay during the follow-up period, including admissions due to complications related to the allocated treatment. The length of initial hospital stay is included but will also be reported separately”

Comment 8: “The discussion does not include a section about faecalith, although this is an exclusion condition worthy of further explanation”

Response 8: We have integrated a part regarding the exclusion of patients with a faecalith in the discussion section.

Page 12 Line 15: “Exclusion of patients with appendiceal faecalith
We excluded patients with a suspicion of an appendiceal faecalith on pre-operative imaging studies because it is associated with a higher failure rate of NOT. Vons et al. reported in the adult population a NOT failure rate after one month of 50% in the group with a faecalith vs. 14% in the group without a faecalith (18). One study only including children with appendicitis and a faecalith on imaging had to terminate inclusions early because of a NOT failure rate of 60% at a median of 4.7 months follow-up (23). Faecaliths are also associated with a higher long term recurrence risk in children, with 47.4% recurrences vs 23.7%(21).

Comment 9: “In addition, the discussion seems to stop rather abruptly without a summing-up sentence or paragraph”

Response 9: We added a new paragraph as a conclusion of the discussion.

Page 13 Line 32: “Unique for the APAC trial is its primary outcome measure; total number of complications after 1 year. Delayed appendectomy or recurrence is not reported as the primary endpoint or as a complication. Because in our opinion there is a place for the appendectomy in non-operative management as a step-up approach for children unresponsive to antibiotic treatment. As a result eight or nine out of every 10 children with uncomplicated appendicitis would no longer have to undergo an appendectomy. Furthermore if we are able to identify specific predictive pre-operative variables, we might identify a group of patients with even better (long-term) outcomes. Finally this trial should answer the question whether the advantages of NOT are also reflected in the reported quality of life and diminished costs.“

Reviewer 2:

Major concern 1A: “This is a very practical and clinical approach as in real life this is what happens. However, I am not sure, whether this is either statistically or form a clinical perspective the optimal setting especially with the primary endpoint being complication rate.”

Response 1A: Determining the appropriate primary outcome measure in studies comparing non-operative treatment versus operative treatment remains challenging. Hall et al identified several outcome measures reported in studies investigating appendicitis. There is a wide variety of outcomes reported. They call for the development of a Core Outcome Set, although till date they are still lacking. Because the choice of our primary outcome is distinctive we added a part discussing our choice of the primary outcome measure. Although other outcomes (such as life-impact) are also of value, at this point, the medical community needs an answer whether the initial non-operative treatment strategy is not worse than the direct appendectomy strategy.

Page 11 Line 38: “Choice of primary outcome
Determining the appropriate primary outcome measure in studies comparing non-operative treatment to operative treatment remains challenging. In our opinion, both strategies will be effective in treating patients with appendicitis, and therefore effectiveness or failure is not an appropriate outcome measure. Therefore we decided to use a composite outcome measure i.e. complications. Such outcome measures (morbidity and mortality) are necessary in order to start the debate whether or not non-operative treatment strategy can be integrated in clinical practice.
Furthermore our goal is to compare the initial non-operative treatment strategy (reserving an appendectomy for those not responding or with recurrent appendicitis) to direct operative treatment strategy. In this view, stating that delayed appendectomy for the indication of failed antibiotic treatment or recurrent appendicitis is a complication would not be appropriate as it is integrated in the treatment strategy. Post-operative complications after delayed appendectomy are however considered as complications of the initial non-operative treatment strategy.

The amount of delayed appendectomies (for both non-responders and recurrent appendicitis) needs be included in the debate whether or not initial non-operative treatment strategy can be implemented in daily practice. It is therefore reported as a secondary outcome."

Major concern 1B: "The authors have stated to perform both ITT and PP analysis, but with a primary endpoint of complication rate, with this trial setting I am concerned for bias in the NOT group"

Response 1B: In non-inferiority research there is a risk of bias towards the alternative hypothesis (stating non-inferiority) if only ITT analysis is performed. Therefore we will report both analyses. If the ITT analysis shows non-inferiority and the PP analysis indicates that NOT is inferior to immediate appendectomy (i.e. more than 5% difference in complication rate in favour of appendectomy), we cannot reject the null hypothesis.
Secondly we have integrated a part in our methods section, defining a protocol crossover. As mentioned, non-operative treatment strategy consist of initial non-operative treatment (i.e. antibiotics) and an appendectomy in case of recurrent or not responding. This means that if in a patient a delayed appendectomy is performed with the indication of clinical deterioration or recurrent appendicitis, this patient will be analyzed both in the ITT en PP analysis in the non-operative treatment strategy group. Only in case a patient will undergo a delayed appendectomy based upon parenteral request, this patient will be analyzed in the PP analysis in the operative treatment group.

Page 9 Line 36: "We only consider cases as a treatment arm crossover if the randomly assigned treatment is switched because of patient and/or parental preference without their being medical grounds. Therefore patients receiving an appendectomy because of clinical deterioration, abdominal complaints after discharge, or recurrent appendicitis will be not be labeled as a crossover."

Major concern 2: "Definitions of the primary outcome in both study groups need to be much more precise in order to enable reliable comparison
a. It is good that delayed appendectomy is not considered a complication (please see 1.) as it is not in this respect evaluating the possibility of treating most of the patients with uncomplicated acute appendicitis with antibiotics instead of surgery.
b. Define allergic reaction; rash?
c. SSI definitions need to be precise and validated
d. Bowel obstruction, imaging or clinical diagnosis or both?
e. Other antibiotic related problems? Diarrhoea? Other abdominal symptoms related to antibiotic use? Nausea? etc.
f. Appendectomy complications: Clavien-Dindo score? "

Response 2: We have defined our outcome measures as appropriate in the method section.

Page 7 Line 51: "The primary outcome is defined as the complication rate at one year follow-up. An independent adjudication committee will review all complications and adverse events to assess their relation to the allocated treatment. The adjudication committee will categorize all complications using the Clavien-Dindo system(30). The Clavien-Dindo system was developed for reporting surgical complications. However, we expect that all possible complications of NOT can also be categorized within the same system, making a comparison between the two groups more consistent. We will report both the overall complication rate as well as subgroups based on complication severity. Complications are defined as, but not limited to:

- Complications of antibiotic use: Allergic reaction with the need for treatment, gastro-intestinal symptoms with the need for treatment, secondary infections, etc.
- Need for surgical or radiological intervention other than appendectomy but related to appendicitis
- Re-admission for an indication other than recurrent appendicitis but related to the allocated treatment
- Complications associated with appendectomy:
- Surgical site infection. Incisional and organ-space as defined by the CDC criteria(31). We do not differentiate between superficial and deep-incisional infection
- Stump leakage/stump appendicitis in need of antibiotic treatment or surgical/radiological intervention
- Secondary bowel obstruction confirmed by imaging or per-operative diagnosis with the need for (non-surgical) treatment. For instance as a result of adhesions.
- Anesthesia related complications, such as pneumonia (in need of antibiotic treatment)
- Incisional hernia. Defined as any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging)"

Minor concern 1: "NOT is not a good abbreviation for non-operative treatment and the abbreviation should be discarded and write out the term"
Response to minor concern 1: We agree that the abbreviation NOT can sometimes get in the way of the readability because of its resemblance to 'not'. However, two out of the three systematic reviews on non-operative treatment of children with appendicitis use the abbreviation NOT, and it is the most commonly used abbreviation in pediatric literature regarding this subject. That is why we choose to not alter the abbreviation.

Minor concern 2: "In the methods section in addition to multiple meta-analysis and the French trial, the authors should discuss all of the existing RCTs on the topic in the adult population including the Swedish studies by Styrud and Hansson and our Finnish APPAC trial. The evaluation of the primary endpoint and the definitions is good to do based on the existing literature."

Response to minor concern 2: It would indeed be best to report on all studies regarding the non-operative management of appendicitis. However this is not the aim of this manuscript. Especially not regarding the adult literature. In the introduction we attempted to show the range of reported outcomes in the adult literature and to show the different interpretations that followed. To report on all existing evidence would substantially lengthen the introduction. We also chose to show studies that reported on rates of complications. Styrud et al did not report complications in the antibiotic group. It is difficult to interpret the reporting of complications by Hansson et al. because of the very high rate of crossovers. The APPAC indeed reports a higher rate of reduction in complications than the trial by Rollins et al. We have altered the text and added the APPAC trial as a reference.

Page 3 Line 33: "Most trials conclude that NOT is safe, but the reported reduction of complications varies from no significant differences(7,8) to up to 86% reduction(9)."

9. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis. JAMA. 2015 Jun 16;313(23):2340.

Minor concern 3: "APAC trial acronym is very close to our APPAC trial acronym and maybe it would be beneficiary to APAC-study to somehow revise their acronym to better state the pediatric patient population in the trial name to be more informative and avoid unnecessary mix-ups.
Response to minor concern 3: There are other similar acronyms which are somewhat confusing as for instance the APPY trial by Shawn St.

Peter et al.. However as our pilot study registered in 2011 was also named the APAC study and the APAC trial has already commenced in over 10 hospitals changing it would result in confusion amongst participating hospitals. Hopefully because of the difference in population with the APPAC trial the confusion will be limited. However we will consider not using the acronym in the title of further publications of our results.

Minor concern 4: “Appendicolith definition in the ultrasound imaging, us criteria for appendicolith?”
Response to minor concern 4: We have added the generally accepted ultrasound criteria for an appendiceal faecalith.

Page 5 Line 10: “Children with a suspicion of an appendiceal faecalith on imaging studies are excluded, because of its association with a higher risk of NOT failure(20–23).
Ultrasound characteristics for an appendicolith are defined as a echogenic, well-defined focus within the appendix with posterior acoustic shadowing.”

Minor concern 5: “More information on the parallel implementation study needs to be stated in the study protocol.”
Response to minor concern 5: We did mention the implementation study as a part of our dissemination plan as we deemed it relevant for the dissemination of the trial results. Since this paper focusses on the protocol of the randomized trial we think that further elaborating on the protocol of the implementation study would not contribute to a clear description of the RCT protocol.

We hope that with these responses we have adequately addressed the concerns posed by the reviewers. Thank you in advance for re-considering this article for publication.

VERSION 2 – REVIEW

REVIEWER	Simon Eaton UCL Great Ormond Street Institute of Child Health SE is an investigator on the APPY trial and the CONTRACT Trial, both of which have similarities to this study design.
REVIEW RETURNED	02-Aug-2017

GENERAL COMMENTS	The authors have responded fully to the concerns that I raised for the initial submitted version of the manuscript.

REVIEWER	Paulina Salminen Turku University Hospital, Finland
REVIEW RETURNED	10-Aug-2017

GENERAL COMMENTS	The authors have made sufficient revisions according to the review suggestions. I have one more minor revision suggestion regarding the signs for clinical deterioration resulting in moving on to surgery from NOT. As for the first three items on that list (Figure 1), no additional definitions are needed. However, the last two criteria would benefit from some clarification as we very well know that in all RCTs evaluating this topic have the tendency towards premature rescue surgery in some patients.

	Even though the possible appendectomy during the initial hospitalization is included in the definition of the NOT group, it will still be of clinical interest and importance to know how many patients actually require surgery during the primary hospitalization as by many colleagues this will be considered a primary treatment failure. How have the surgeons treating the APAC study patients been informed of these criteria or are all patients evaluated by surgeons in the research group to avoid this possible attitude driven tendency to offer surgery at a too early phase? Rising WBC/CRP level: Both levels rising or just the other? Which one is more important; most often, as we all know, WBC is already declining the next morning, but CRP may very well be much higher than on admission? Any % or cut-off levels? Increasing level of pain: same criteria (NRS and total usage of pain medication)? It would be good to add some information regarding this topic and to clarify the decision making process in moving on to surgery during the initial hospitalization.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2:

Minor revision 1: I have one more minor revision suggestion regarding the signs for clinical deterioration resulting in moving on to surgery from NOT. As for the first three items on that list (Figure 1), no additional definitions are needed. However, the last two criteria would benefit from some clarification as we very well know that in all RCTs evaluating this topic have the tendency towards premature rescue surgery in some patients. Even though the possible appendectomy during the initial hospitalization is included in the definition of the NOT group, it will still be of clinical interest and importance to know how many patients actually require surgery during the primary hospitalization as by many colleagues this will be considered a primary treatment failure. How have the surgeons treating the APAC study patients been informed of these criteria or are all patients evaluated by surgeons in the research group to avoid this possible attitude driven tendency to offer surgery at a too early phase?

Rising WBC/CRP level: Both levels rising or just the other? Which one is more important; most often, as we all know, WBC is already declining the next morning, but CRP may very well be much higher than on admission? Any % or cut-off levels?

Increasing level of pain: same criteria (NRS and total usage of pain medication)?

It would be good to add some information regarding this topic and to clarify the decision making process in moving on to surgery during the initial hospitalization.

Response 1: The preemptive choice for surgery is indeed reason for caution. In our protocol the criteria for clinical deterioration are defined more in detail. We have added these definitions to the manuscript. Regarding the decision-making. The decision to proceed with urgent appendectomy ultimately lies with the surgeon in charge of the patients care. However another appropriate course of action would be to procure additional imaging to aid in this decision. As said, the decision lies with treating surgeon, however, it is encouraged to consult the surgeons of the research team. In our experience this is always the case. The clinical deterioration criteria are in place to aid in the decision making, however in the end the decision to choose for appendectomy will always remain a clinical judgement. We do not encourage surgeons to base their decision solely lab results or measurements. We have adjusted the text in order to further clarify the decision-making in our trial.

Page 6 Line 48: “Pre-defined criteria are in place to define the indication for appendectomy (Figure 1). In detail: a WBC count of more than 20 10E9/L or an increasing WBC count after 48 hours are criteria for clinical deterioration. As well as increasing CRP levels after 48 hours. An increasing pain level is defined as a higher NRS score than on admission despite of adequate pain medication according to protocol.
If the patient meets any of these criteria, the decision can be made to proceed with urgent appendectomy or to perform additional imaging studies. This decision is at the discretion of the surgeon in charge of the patients care and does not lie with study coordinators. However, it is common practice for the treating surgeon to consult with the study coordinators on the appropriate course of action.”

We hope that with this response we have adequately addressed the concern posed by the reviewer. Thank you in advance for re-considering this article for publication.

VERSION 3 – REVIEW

REVIEWER	Paulina Salminen Turku University Hospital, Finland
REVIEW RETURNED	13-Sep-2017

GENERAL COMMENTS	The authors have added definitions for the criteria (rising WBC/ CRP and increasing level of pain) in moving on to surgery or not.